Studies on the Synthesis and Reactivity of Fused 3,4-Isoxazoles

by

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1993

CONTENTS

DECLARATION

I declare that this thesis is of my own composition, that the work of which it is a record was carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1990 and September 1993.

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POSTGRADUATE LECTURE COURSES ATTENDED

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Twenty-first Scottish Regional Meeting (1992), University of Edinburgh.

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"Discovery, Development and Pharmacology of Zoladex for the treatment of Prostate Cancer": 1992; various lecturers from ICI Pharmaceuticals Division.

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"Reasearch and Development in the Pharmaceutical Industry": 1993; Professor A. McKillop, University of East Anglia.

ABSTRACT

This thesis is concerned with the synthesis of various fused 3,4-isoxazoles by the thermal cyclisation of 2-nitroaryl and 2-nitroheteroaryl acetic acid derivatives and the exploitation of the uses of these compounds in heterocyclic synthesis by their reduction to afford 2-aminoaryl and heteroaryl ketones followed by the annulation of these latter derivatives.

Heating solutions of 2-(3-nitropyrid-2-yl)propanedioate esters under reflux in inert solvents afforded isoxazolo[4,3-b]pyridine-3-carboxylate derivatives. The successful application of this novel synthesis on a large scale was crucially dependant on the physical removal of the corresponding alcohol component from the reaction mixture. The thermal cyclisation of various 2-substituted 2-(3-nitropyrid-2-yl)ethanoates was also examined and in the case of cyano derivatives afforded the anticipated isoxazolo[4,3-b]pyridines but was less successful for substrates containing keto groups. 2-(3-Nitropyrid-2-yl)ethanoate failed to cyclise to afford the parent isoxazolo[4,3-b]pyridine. Evidence is presented for the involvement of ketene intermediates in these thermal cyclisation reactions.

Reduction of the isoxazolo[4,3-b]pyridine-3-carboxylate derivatives gave either 2-(3-aminopyrid-2-yl)-2-hydroxyethanoate or 2-(3-aminopyrid-2-yl)-2-oxoethanoate derivatives depending on the substrate, the former compounds being converted into the latter by oxidation with manganese dioxide. Annulation of the 2-(3-aminopyrid-2-yl)-2-oxoethanoates produced then gave a variety of substituted 1,5-napthyridin-2(1H)-one derivatives. The chemical transformations of these new 1,5-napthyridine derivatives was also briefly examined.

1,7-Napthyridin-2(1H)-one derivatives were also prepared by a similar sequence of reactions commencing with the thermal cyclisation of diethyl 2-(3-nitropyrid-4-yl)propanedioate to give ethyl isoxazolo[3,4-c]pyridine-3-carboxylate

followed by reductive ring opening of the latter and subsequent annulation of ethyl 2-(3-aminopyrid-4-yl)-2-oxoethanoate so produced

A variety of novel ethyl isoxazolo[4,3-d]pyrimidine-3-carboxylate derivatives were prepared by the thermal cyclisation of different diethyl 2-(5-nitropyrimid-4-yl)propanediotes and in one case reduction to afford an ethyl 2-(5-aminopyrimidin-4-yl)-2-oxoethanoate derivative followed by annulation afforded a number of new substituted pyrido[2,3-d]pyrimidines.

The thermal cyclisation of diethyl 2-(2-nitrophenyl)propanedioate derivatives to afford 2,1-benzisoxazole-3-carboxylates was also examined and found to be a slower and lower yielding process than that of the corresponding pyridine and pyrimidine derivatives.

The oxidation of various dialkyl 2-(3-nitropyridyl)propanedioates using a variety of oxidising agents afforded the corresponding dialky 2-hydroxy-2-(3-nitropyridyl)propanedioates. The application of this oxidation procedure to 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile provided an expeditious and high yielding route to the hitherto elusive 3-nitropyridine-2-carboxylic acid. The chemistry of this compound was the subject of a brief investigation in the course of which it was converted into a variety of novel 1-hydroxypyrido[2,3-d]pyrimidine derivatives.

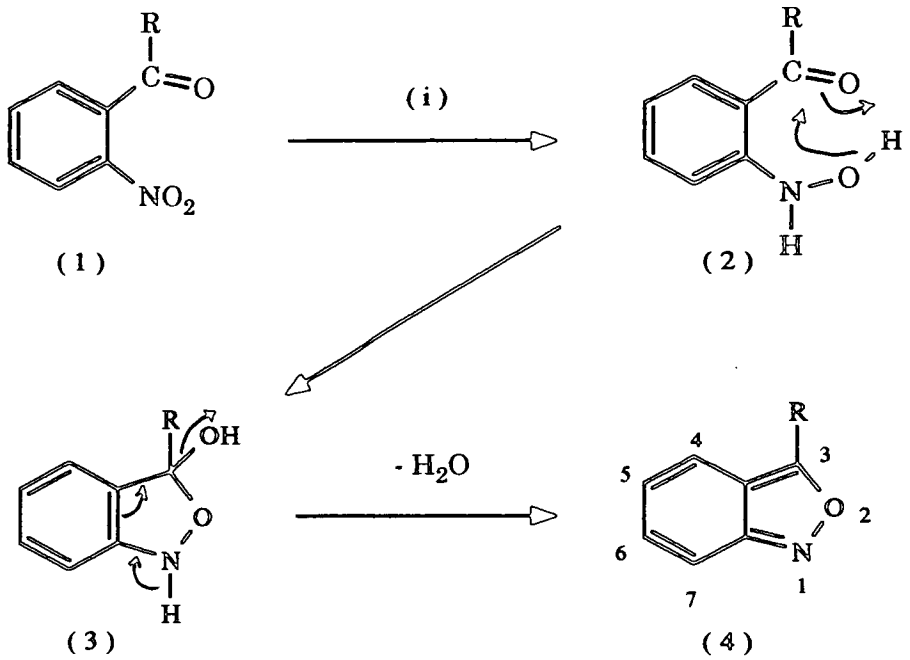
PREFACE

Benzene fused 3,4-isoxazoles (2,1-benzisoxazoles) have been described in the literature since 1882.[2] However no satisfactory general route to heteroaromatic fused 3,4-isoxazoles exists to date and hence very few such heterocycles are known.[1] 2,1-Benzisoxazoles are precursors, through their reduction, of 2-amino acylbenzene derivatives which have many uses in heterocyclic synthesis.[38] Therefore, it was of interest to develop strategies for the synthesis of heteroaromatic fused 3,4-isoxazoles.

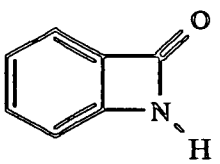
The following thesis is concerned with the development of a new general method for the synthesis of heteroaromatic fused 3,4-isoxazoles and the investigation of the further uses of these compounds in heterocyclic synthesis. By way of introduction, Chapter 1 provides a survey of the existing methods available for the synthesis of fused 3,4-isoxazoles reported in the literature to date and a review of the known reactivity of such heterocycles. This is followed in Chapters 2 to 4 by an account of the results obtained in the present studies.

Chapter 1

A Survey of the Synthesis and Reactivity of Fused 3,4-Isoxazoles



(1) (2) (3) (4)



(5)

(i) reduction.

R
a ; H
b ; Ph

Scheme 1

1 : A Survey of the Synthesis and Reactivity of Fused 3,4-Isoxazoles

1.1 : Introduction

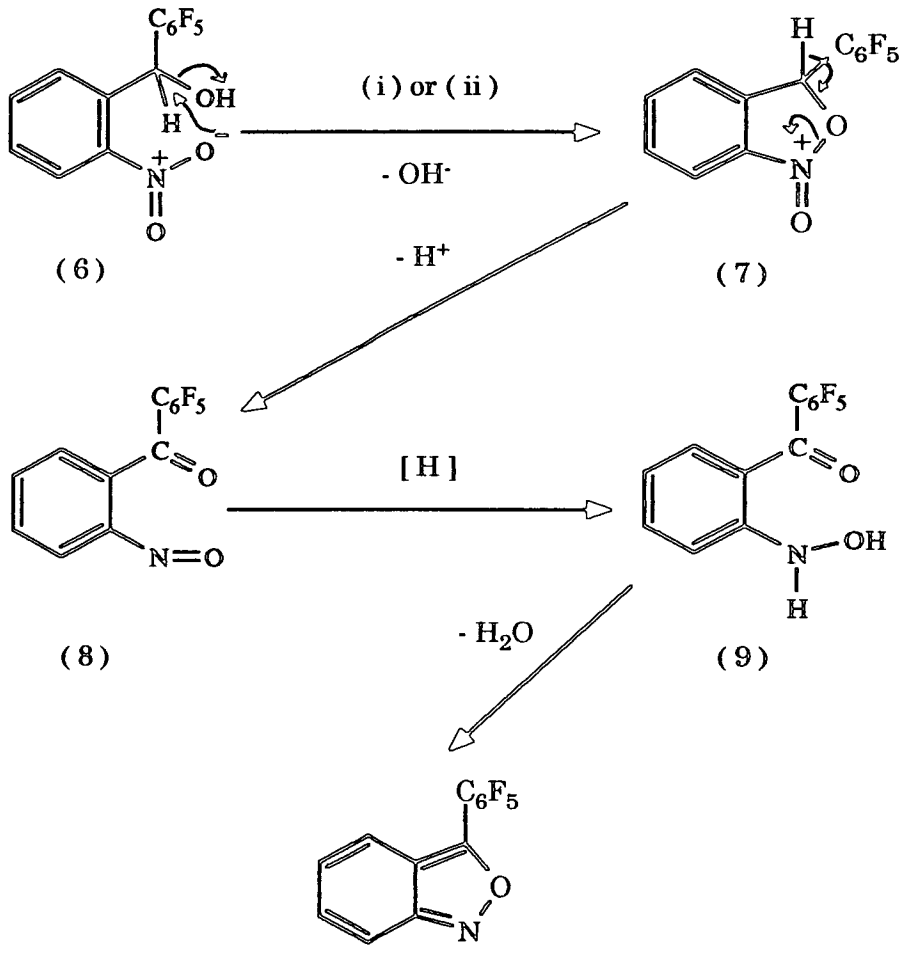
The following survey is concerned with the synthesis and chemical reactivity of fused 3,4-isoxazoles. It is not intended to be an exhaustive account of these topics but instead aims to highlight some of the more important and interesting chemistry of these heterocyclic derivatives. This survey concentrates on the synthesis and reactivity of benzene-fused 3,4-isoxazoles (2,1-benzisoxazoles) since these have been by far the most widely studied fused 3,4-isoxazole derivatives.

The chemistry of fused 3,4-isoxazoles has been the subject of two comprehensive reviews[1] that cover most aspects concerning the synthesis and reactivity of these heterocycles up to 1979. For the sake of brevity, selected areas of fused 3,4-isoxazole chemistry have been excluded from the present survey, namely those concerned with partially or fully saturated fused 3,4-isoxazoles, fused 3,4-isoxazolin-5-ones and fused 3,4-isoxazoloquinones all of which are discussed in the two aforementioned reviews.[1] The photochemically induced syntheses and transformations of fused 3,4-isoxazoles have also been excluded since these are generally low yielding and furnish a plethora of products.

Pertaining to the reactivity of fused 3,4-isoxazoles, the straightforward chemical transformations of substituents on the heterocycle are also outwith the scope of the present survey.

1.2 : The Synthesis of Fused 3,4-Isoxazoles

The first synthesis and identification (Scheme 1) of 2,1-benzisoxazole (4a) was reported in 1882 by Friedländer and Henriques[2] who obtained this heterocycle by the reduction of 2-nitrobenzaldehyde (1a) with tin and acetic acid. At the time



(i) liquid paraffin, 165°.

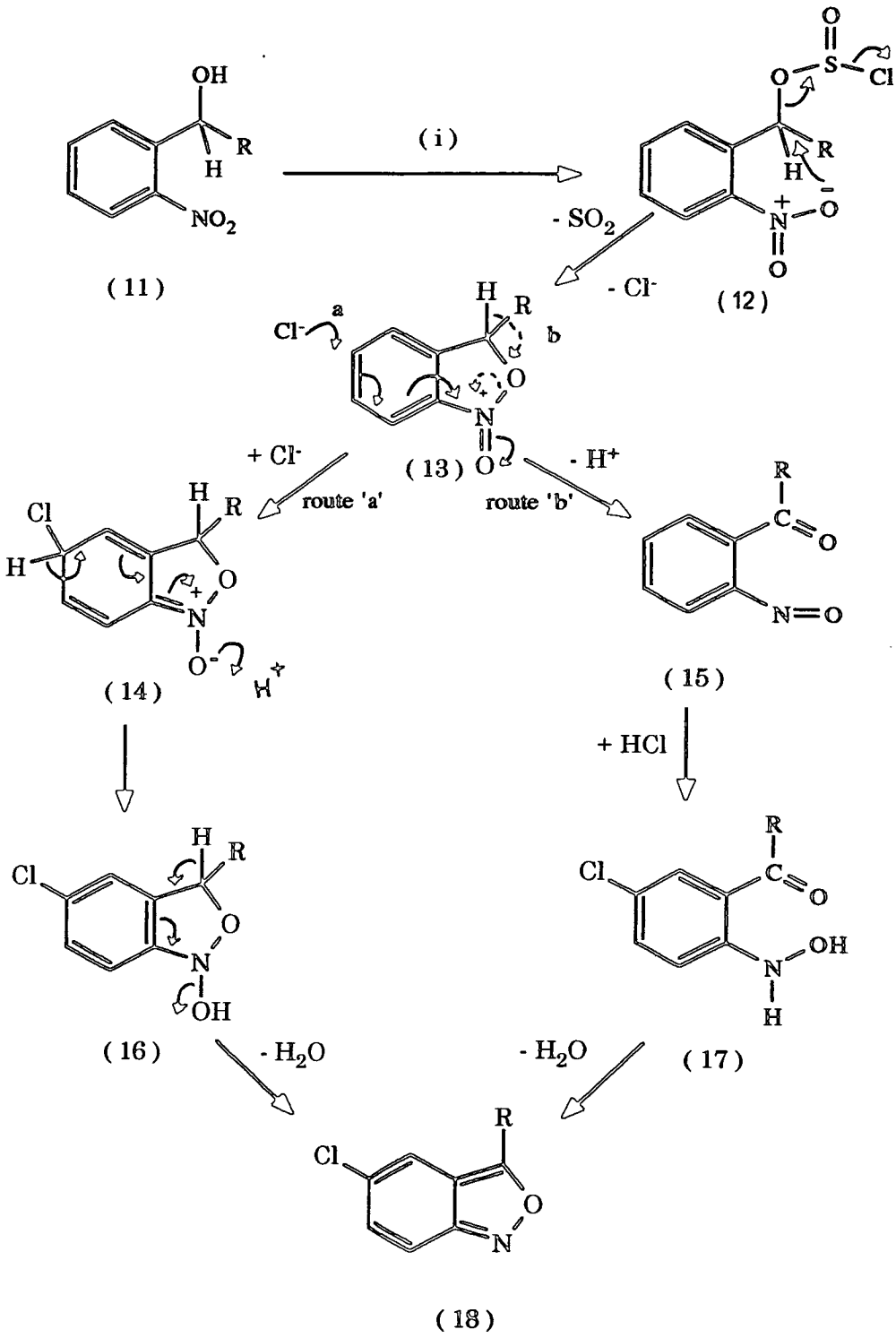
(ii) conc. H_2SO_4, 100°.

Scheme 2

the reduced product was incorrectly thought to have the structure (5) which can be considered as the product arising from intramolecular dehydrative cyclisation of anthranilic acid (2-aminobenzoic acid) hence the trivial name "anthranil" for the product. The structure (4) was later established unequivocally and an interesting account of the controversy surrounding the structure of the "anthranils" at the turn of the century is given in the review by Wunsch and Boulton.[1]

A diverse range of reducing agents has been employed in the reduction of a vast array of 2-nitroacylbenzenes (1) to afford 2,1-benzisoxazoles (4), the full list of which is too large to reproduce here. A typical example is provided by the reduction of 2-nitrobenzophenone (1b) with tin and acetic acid to afford 3-phenyl-2,1-benzisoxazole (4b).[3] This type of heterocyclisation is thought to occur through partial reduction of the nitro group in (1) to give a hydroxylamino species (2), which can then condense intramolecularly with the adjacent carbonyl group before further reduction of the hydroxylamino group can take place, affording the intermediate (3). Finally, dehydration of (3) furnishes the 2,1-benzisoxazole derivative (4).

2,1-Benzisoxazoles have also been synthesised from a wide range of 2-nitrobenzyl alcohol derivatives. For instance (Scheme 2), heating in an inert solvent at 165° or in sulphuric acid at 100° induces the 2-nitrobenzhydrol derivative (6) to cyclise affording 3-(pentafluorophenyl)-2,1-benzisoxazole (10).[4] The exact mechanism of the transformation [(6) → (10)] is unknown but is believed to involve initial nucleophilic displacement of the benzylic hydroxyl group by the nitro group to give a bicyclic intermediate (7). This can subsequently form the 2-nitrosobenzophenone derivative (8) which in some way is then reduced to the hydroxylamine (9) perhaps by unreacted benzhydrol (6), which itself would suffer concomitant oxidation to 2-nitropentafluorobenzophenone. This siphoning off of the starting material may be the reason for the low yields observed in this reaction.[4] The hydroxylamine (9) so formed can furnish the 2,1-benzisoxazole (10) by



(i) $SOCl_2$, reflux.

R

a ; Ph

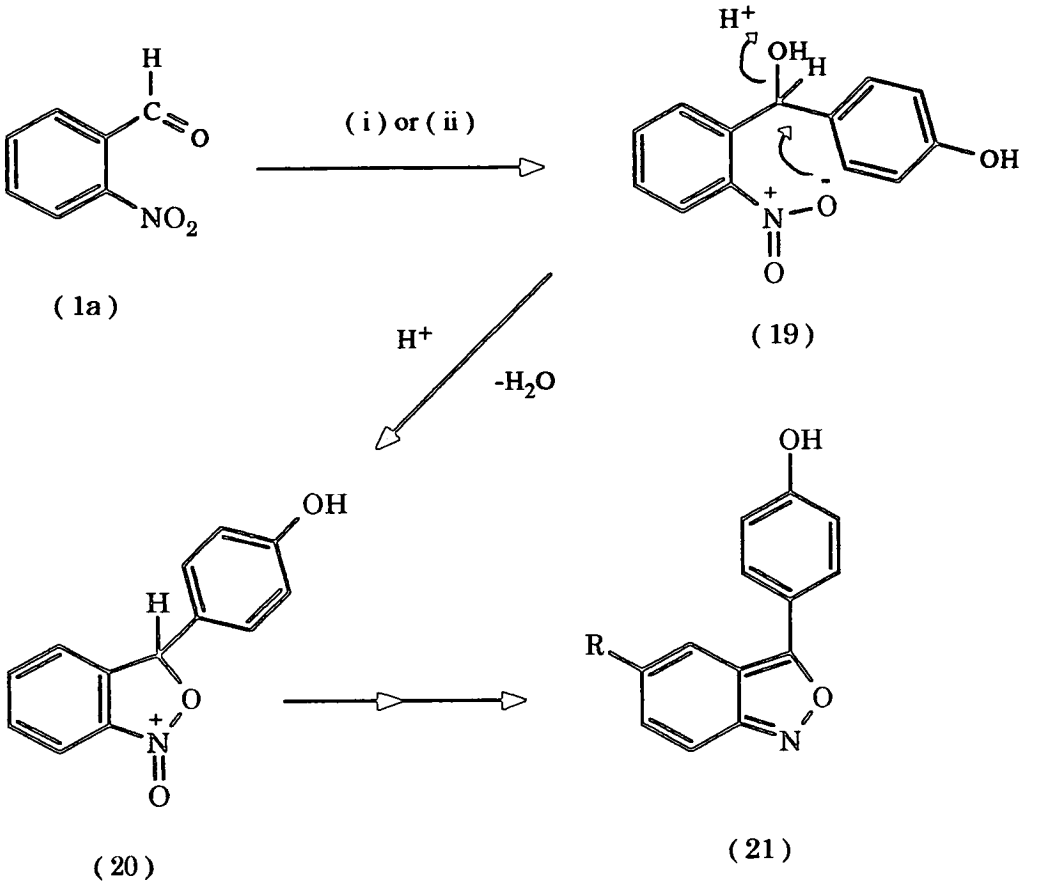
b ; CO_2Me

Scheme 3

dehydration in a fashion similar to that described before [see Scheme 1; (2) → (3) → (4)]. This 2,1-benzisoxazole synthesis should therefore be promoted by enhancing the leaving group capacity of the hydroxyl group in (6) and this is indeed demonstrated by the successful cyclisation of (6) to (10) in hot sulphuric acid solution. Further evidence for this mechanistic pathway is provided by the fact that the tosylate derived from (6) is converted into (10) in refluxing toluene solution.[4]

Thionyl chloride is also known to convert 2-nitrobenzylalcohols into fused 2,1-benzisoxazoles (Scheme 3) accompanied by the intriguing introduction of chlorine into the aromatic nucleus.[5,6] In refluxing thionyl chloride solution the alcohols (11a) and (11b) cyclise to give 5-chloro-3-phenyl-2,1-benzisoxazole (18a)[5] and methyl 5-chloro-2,1-benzisoxazole-3-carboxylate (18b)[6] respectively. The authors suggest that the these transformations are initiated by the formation of a chlorosulphite ester (12), thus creating a good leaving group at the benzylic position, followed by its nucleophilic displacement by the nitro group to afford the intermediate (13). This intermediate can then furnish the 2,1-benzisoxazole (18) by one of two possible routes. The authors propose[6] that attack by chloride ion on (13) affords (14), which then aromatises to give the bicyclic intermediate (16), followed by final dehydration of the latter to yield the product (18). Alternatively, the bicyclic intermediate (13) can deprotonate to form the nitrosoketone intermediate (15). Reduction of the nitroso group to a hydroxylamine can then be achieved with accompanying entry of chlorine into the aromatic nucleus to furnish (17). Precedent for this mode of reduction is found in Bamberger's observation[9] that treatment of nitrosobenzene with hydrogen chloride affords 4-chlorophenylhydroxylamine. Final cyclisation of (17) in a previously described manner [see Scheme 1, (2) → (3) → (4)] then affords the 2,1-benzisoxazole (18).

Similarly, the intermediacy of a benzylic alcohol has been proposed (Scheme 4) during the hydrogen chloride catalysed reaction of 2-nitrobenzaldehydes with phenol derivatives to afford 3-aryl-2,1-benzisoxazoles.[7,8] Thus when an ethereal



(i) PhOH, HCl, Et_2O.

(ii) PhOH, HBr, Et_2O.

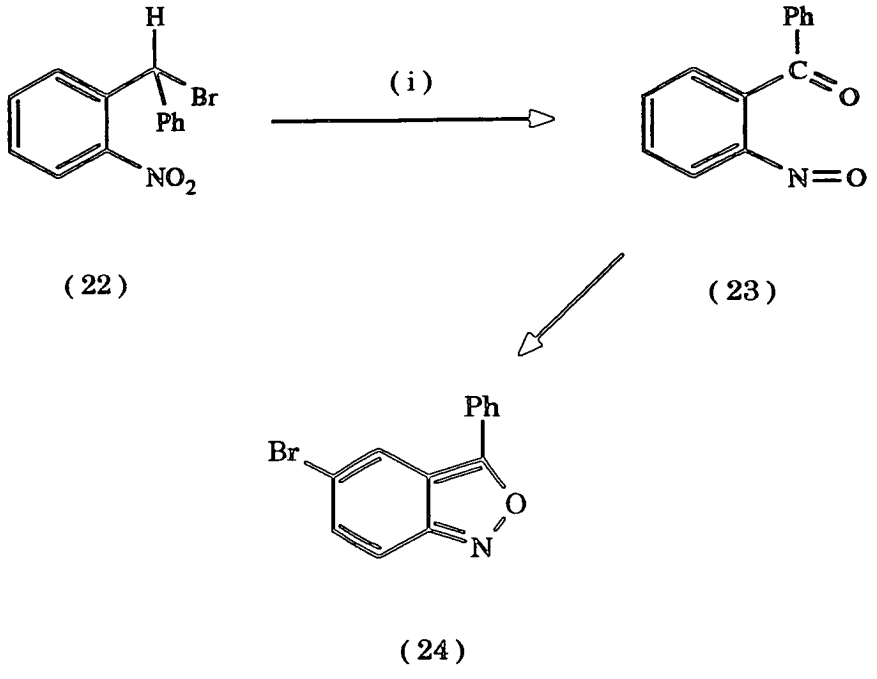
R

a ; Cl

b ; Br

c ; H

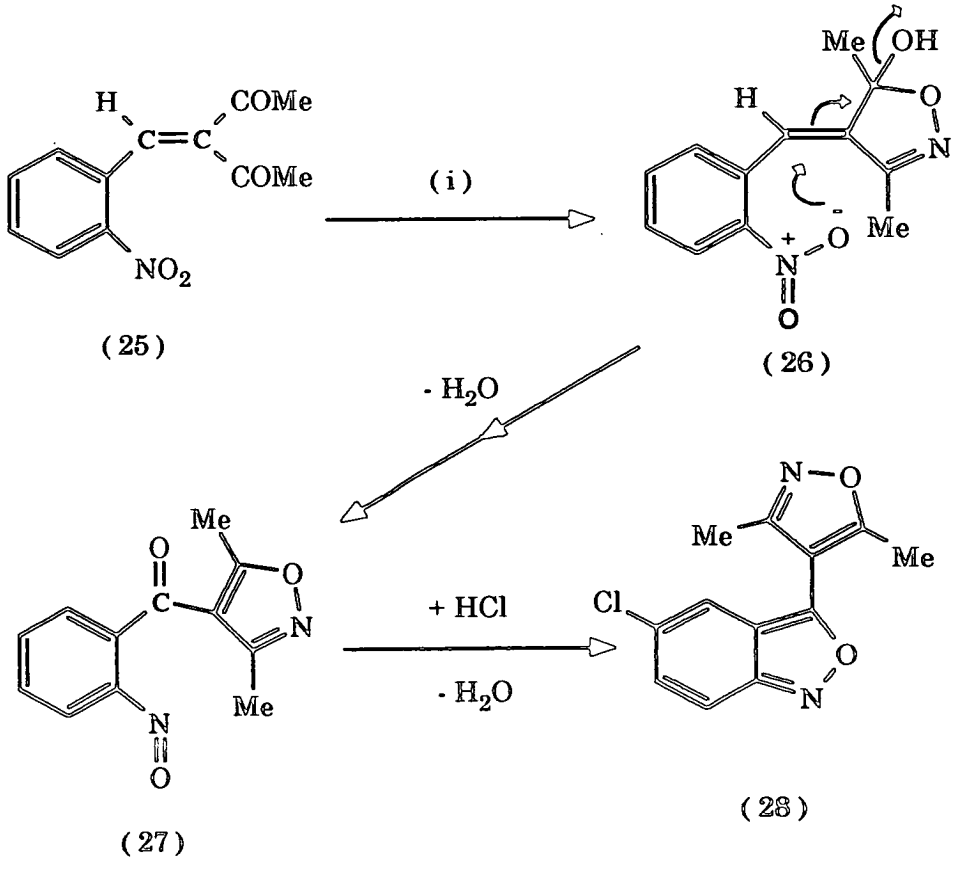
Scheme 4



(22) (23) (24)

(i) AcOH, 45°.

Scheme 5



(25) (26) (27) (28)

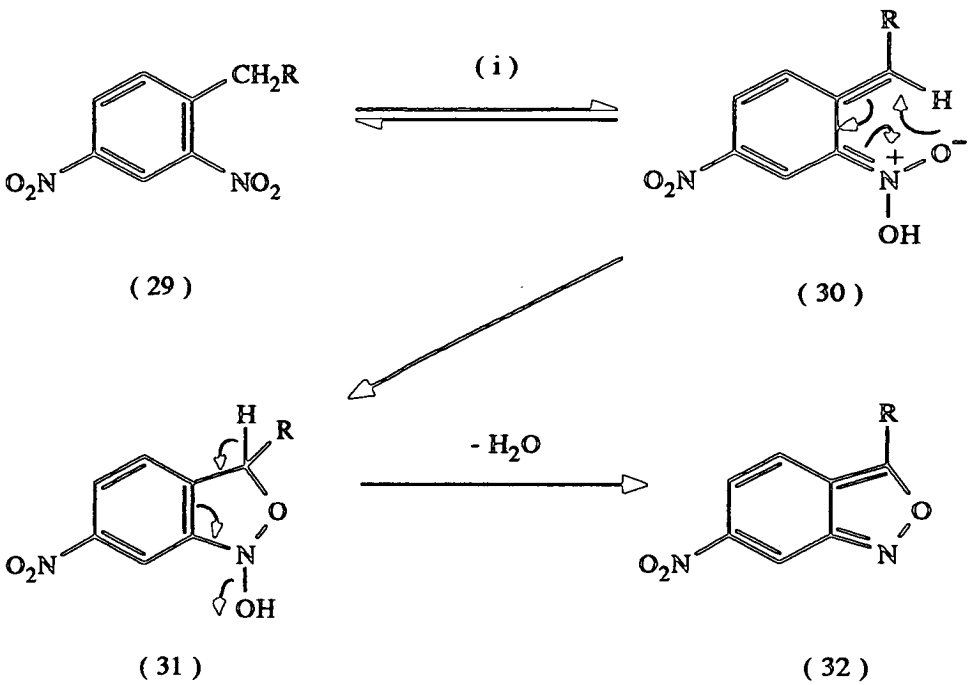
(i) NH_2OH . HCl, AcOH, 50°.

Scheme 6

solution of 2-nitrobenzaldehyde (1a) and phenol is saturated with gaseous hydrogen chloride, a near quantitative yield of 5-chloro-3-(4'-hydroxyphenyl)-2,1-benzisoxazole (21a) is obtained.[7] The intermediacy of benzhydrol (19) is proposed[7] which then cyclises as shown to afford (20). This intermediate (20) can then furnish the 5-chloro-3-(4'-hydroxyphenyl)-2,1-benzisoxazole (21a) by a sequence of transformations similar to those described in Scheme 3 [(13) → (18)]. The authors also found that hydrogen bromide catalysed this 2,1-benzisoxazole synthesis[7] although with this reagent a mixture of the 5-bromo (21b) and the 5-unsubstituted (21c) 2,1-benzisoxazoles was formed. This result demonstrates that hydrogen bromide is somehow able to achieve an alternative mode of reduction without entry of halogen into the aromatic ring. This evidence therefore favours the nitroso to hydroxylamine pathway [see Scheme 3, (15) → (18)] over the alternative route [(13) → (14) → (18)] but a combination of the two cannot be ruled out.

Another similar example (Scheme 5) is the conversion of 2-nitrobenzhydryl bromide (22) into 5-bromo-3-phenyl-2,1-benzisoxazole (24) by simply warming in glacial acetic acid.[10] Displacement of the benzylic bromine by the nitro group followed by a sequence of steps similar to those shown in Scheme 3 [(13) → (15) → (17) → (18)] finally leads to 5-bromo-3-phenyl-2,1-benzisoxazole (24). Sodium acetate added to the reaction mixture removes the extruded hydrogen bromide and allows the isolation of the intermediate 2-nitrosobenzophenone (23). Subsequent treatment of (23) with hydrogen bromide in acetic acid results in the rapid formation of the 5-bromo-2,1-benzisoxazole (24), all of which evidence supports the proposed reaction mechanism.

2-Nitrobenzylidene derivatives have also been cyclised to afford 2,1-benzisoxazoles.[11,12] For example (Scheme 6), 2-nitrobenzylidene acetylacetone (25) yields the 3-substituted 5-chloro-2,1-benzisoxazole derivative (28) when treated with hydroxylamine hydrochloride.[11] This interesting reaction is similar to those illustrated in Schemes 2 - 5 in so far as the proposed intermediate (26) from the



(i) H_2SO_4 (conc.), heat.

R

a ; $COCH_3$

b ; CO_2H

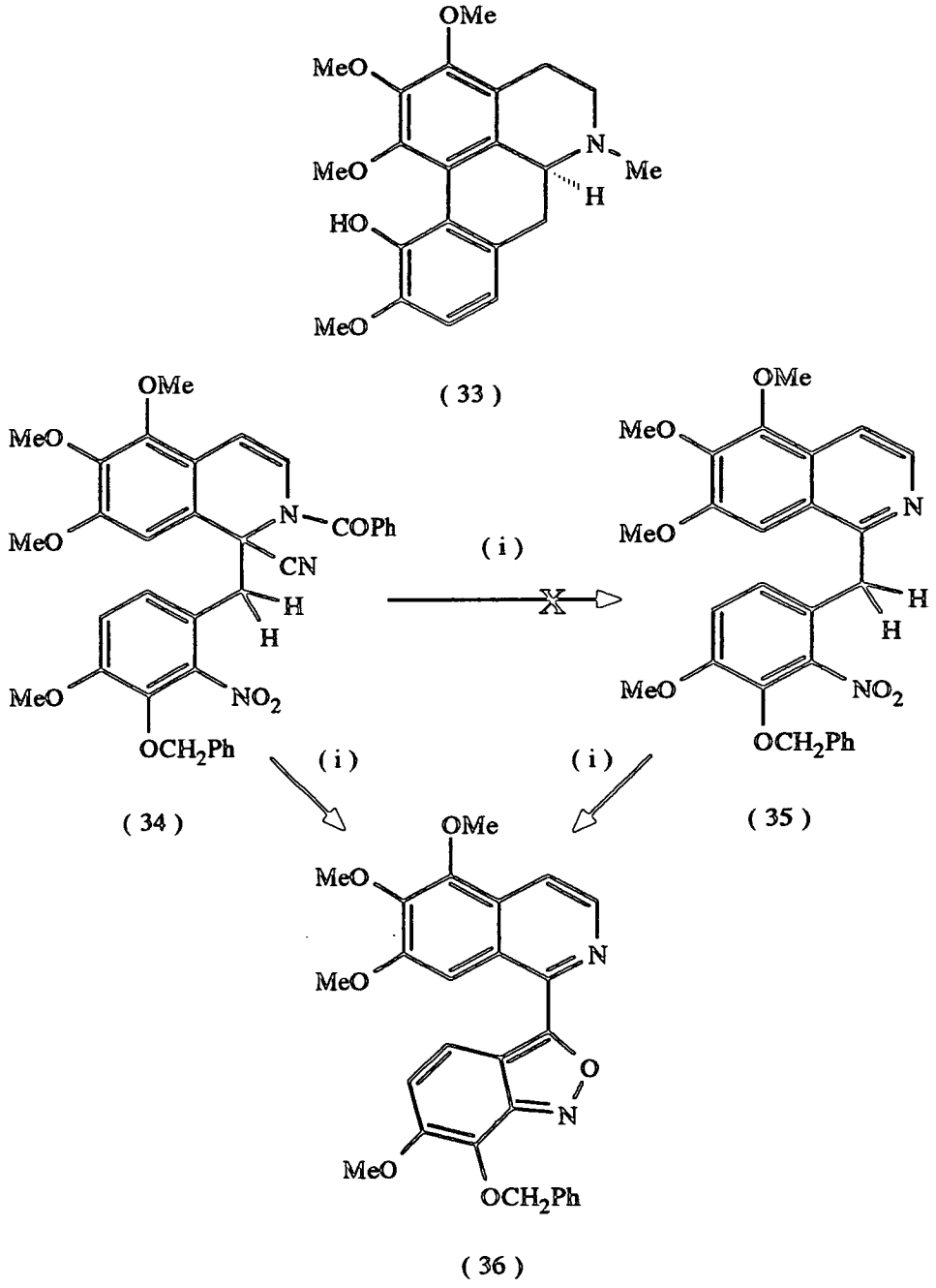
c ; H

Scheme 7

reaction of (25) with hydroxylamine is a vinylogous benzylic alcohol. Participation of the nitro group in the displacement of the vinylogous hydroxyl group, as shown for (26), leads to the nitroso intermediate (27) which, in a similar fashion to that illustrated in Scheme 3, can be converted into the 5-chloro-2,1-benzisoxazole (28) in the presence of hydrogen chloride.

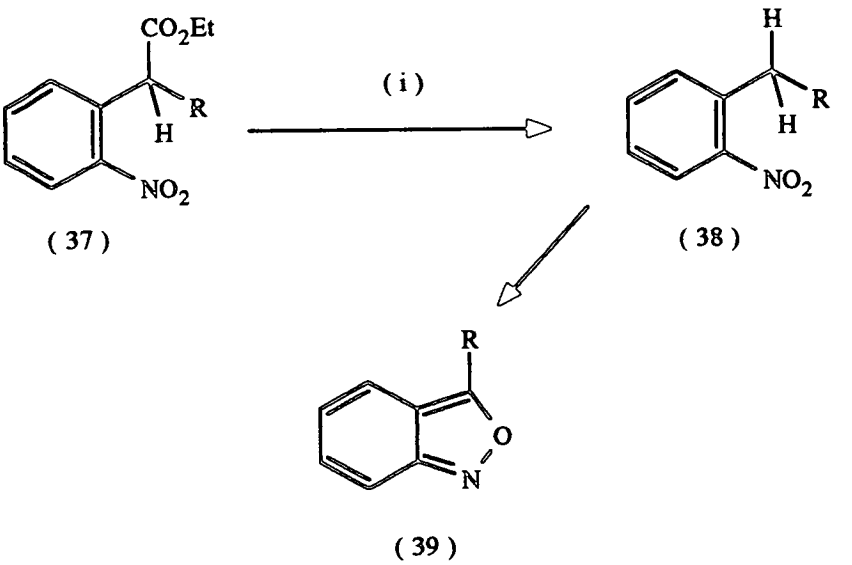
A variety of 2-nitrobenzyl derivatives substituted with electron withdrawing groups have been cyclised under acidic and basic conditions or thermally to afford 2,1-benzisoxazoles.[8] This is exemplified by the transformation (Scheme 7) of 2,4-dinitrophenylacetone (29a) in concentrated sulphuric acid at 110° into 6-nitro-2,1-benzisoxazole (32c),[13] the 3-unsubstituted product presumably arising by deacylation of the initially formed 3-acetyl derivative (32a). In a similar fashion, heating 2,4-dinitrophenylacetic acid (29b) in concentrated sulphuric acid at 120° furnishes a mixture of 6-nitro-2,1-benzisoxazole-3-carboxylate (32b) and 6-nitro-2,1-benzisoxazole (32c),[14] the latter product presumably arising via decarboxylation of the former. It has been suggested by the authors that these acid catalysed reactions proceed through cyclisation of the initially formed aci-nitro tautomer (30) to a bicyclic intermediate (31) which can then dehydrate as shown to afford the final 2,1-benzisoxazole products (32).

An interesting example of the base catalysed formation of 2,1-benzisoxazoles from 2-nitrobenzyl derivatives can be found in the field of alkaloid synthesis (Scheme 8).[15] During their studies on the synthesis of Oconovine (33), the authors were attempting the hydrolysis of the Reissert compound (34) to the isoquinoline derivative (35) using ethanolic potassium hydroxide. Unexpectedly, the product of this reaction, which was isolated in high yield, was identified as the 3-isoquinolyl-2,1-benzisoxazole (36). This product was presumably formed by cyclisation of the desired intermediate (35), a conjecture which was substantiated by the independent conversion of (35) into (36) under identical basic conditions. The transformation



(i) KOH, EtOH, reflux.

Scheme 8



(37)

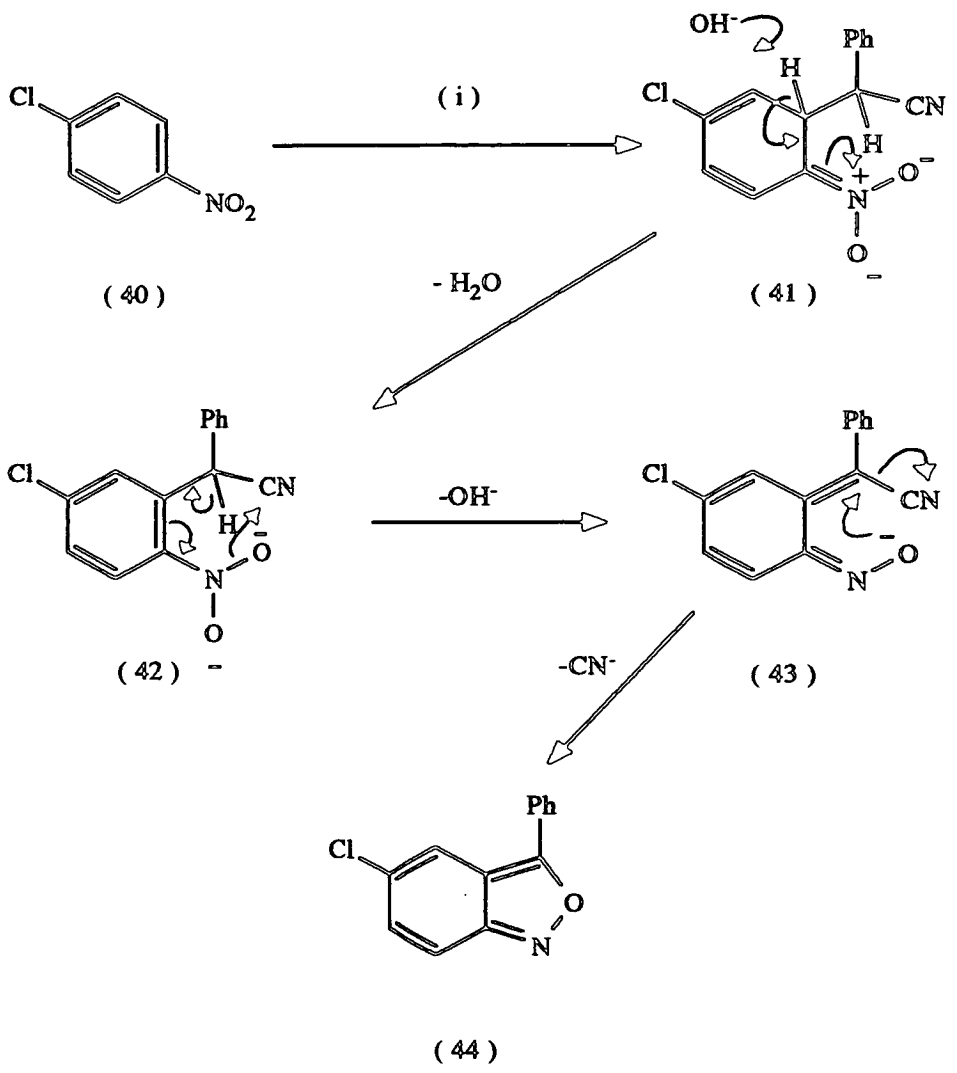
(38)

(39)

(i) heat.

R
a ; CN
b ; CO_2Et

Scheme 9



(i) $PhCH_2CN$, KOH, MeOH, 5°.

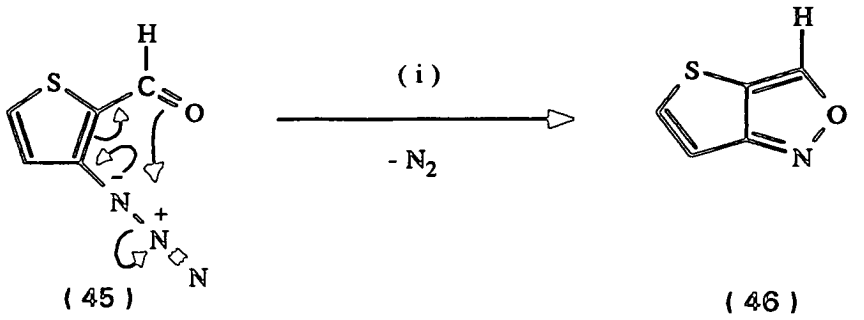
Scheme 10

[(35) → (36)] probably occurs via cyclisation of an aci-nitro intermediate in a similar manner to that proposed in Scheme 7.

The 3-substituted 2,1-benzisoxazoles (Scheme 9) (39a) and (39b) were obtained, albeit in low yield, during the attempted purification by distillation of ethyl 2-cyano-2-(2-nitrophenyl)acetate (37a) and diethyl 2-(2-nitrophenyl)malonate (37b) respectively.[16] The authors suggest that the thermal decarbethoxylation of (37) to give the monosubstituted 2-nitrobenzyl compounds (38) is the first step in this transformation followed by cyclisation of the thermally produced aci-nitro tautomer of (38) in a manner similar to that proposed earlier [see Scheme 7, (30) → (32)] to afford the 2,1-benzisoxazoles (39).

A further interesting and useful synthesis of 2,1-benzisoxazoles involves the base catalysed reaction between nitrobenzenes and arylacetonitriles. This is exemplified (Scheme 10) by the potassium hydroxide catalysed reaction of phenylacetonitrile with 4-chloronitrobenzene (40) to furnish 5-chloro-3-phenyl-2,1-benzisoxazole (44).[17] The authors propose that the mechanism of this process firstly involves attack of the anion of the arylacetonitrile at the ortho position to the nitro group to afford the intermediate (41). Subsequent dehydration of (41) then affords the intermediate (42) which can undergo further transformation to afford (43) which by loss of cyanide ion finally yields the 2,1-benzisoxazole derivative (44).

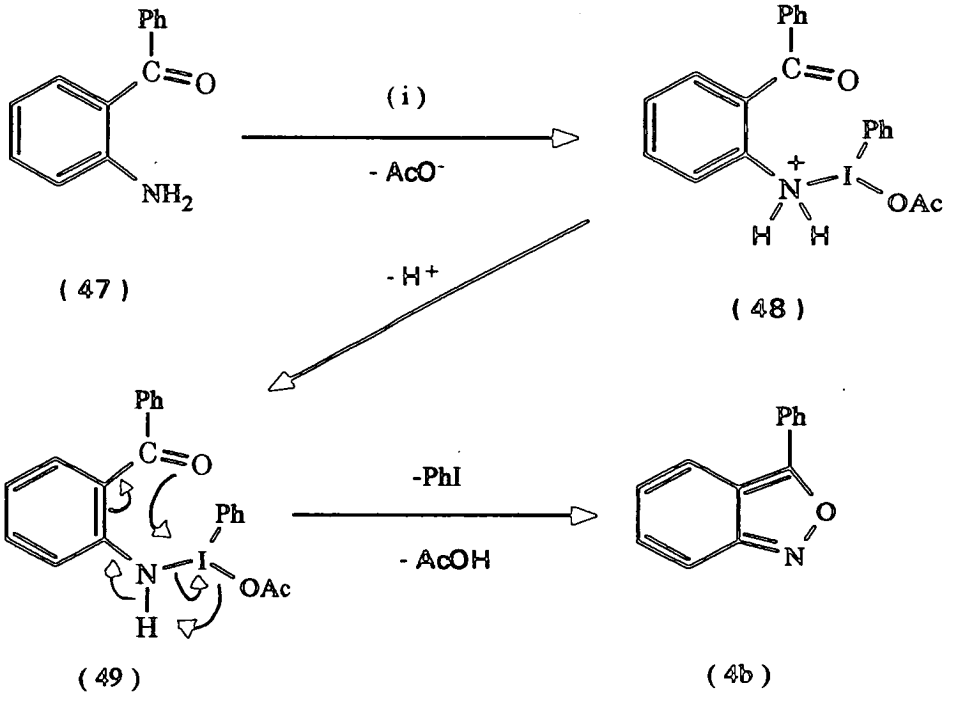
Although nitrobenzenes are by far the most common precursors of fused 3,4-isoxazoles they are not the sole progenitors of these heterocycles. Another common method for the synthesis of fused 3,4-isoxazoles is via the thermolysis and subsequent cyclisation of aromatic 2-acylazides. As an example (Scheme 11), the hitherto inaccessible thieno[3,2-c]isoxazole (46) was readily prepared through the thermolysis of 3-azidothiophene-2-carboxaldehyde (45) in refluxing xylene solution.[18] Kinetic studies on the thermal decomposition of phenylazide derivatives indicate that this cyclisation process proceeds through a concerted mechanism rather



(45) (46)

(i) xylene, reflux.

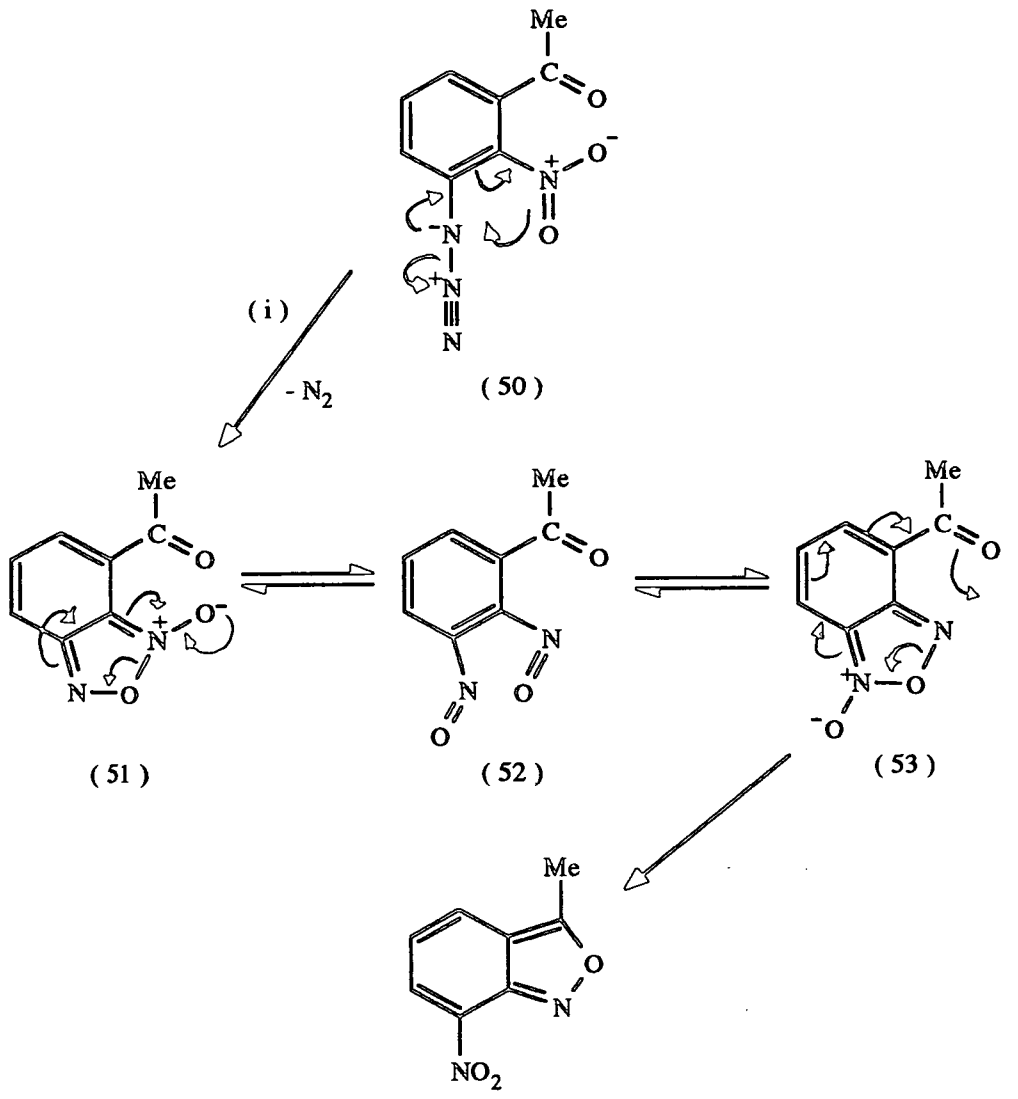
Scheme 11



(47) (48) (49) (4b)

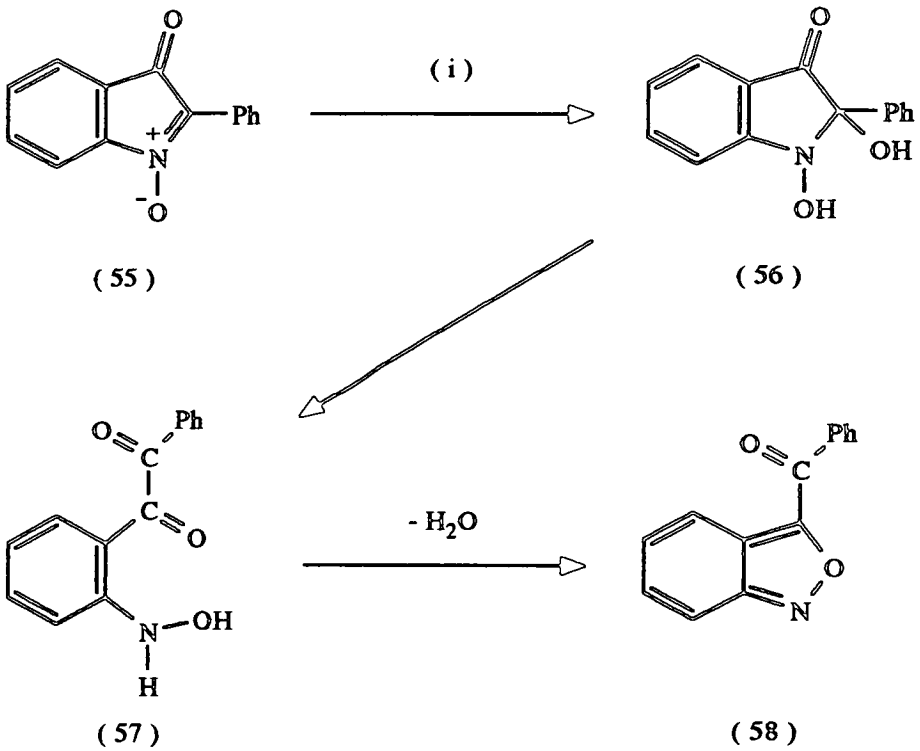
(i) $PhI(OAc)_2$, benzene, 25°.

Scheme 12



(i) heat.

Scheme 13



(i) H_2SO_4, H_2O.

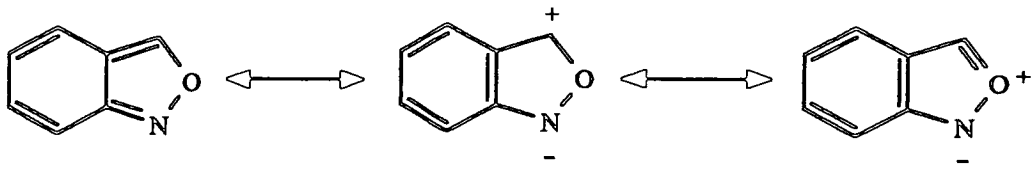
Scheme 14

than one involving a free nitrene and the authors propose that a 6π pericyclic process, as shown for (45), operates.[19]

A less common method for the synthesis of 2,1-benzisoxazoles is via the oxidation of 2-aminoacylbenzenes (Scheme 12). The introduction of phenyl iodosodiacetate as oxidant has greatly increased the potential of this cyclisation as exemplified by the formation of 3-phenyl-2,1-benzisoxazole (4b) in 81% yield by the oxidation of 2-aminobenzophenone (47).[20] The authors propose the initial formation of intermediates such as (48) then (49) in the oxidative pathway, followed by cyclisation with loss of iodobenzene and acetic acid, to yield the 2,1-benzisoxazole (4b) in a fashion not dissimilar to the thermal cyclisation of aromatic 2-acylazides [Scheme 11; (45)].

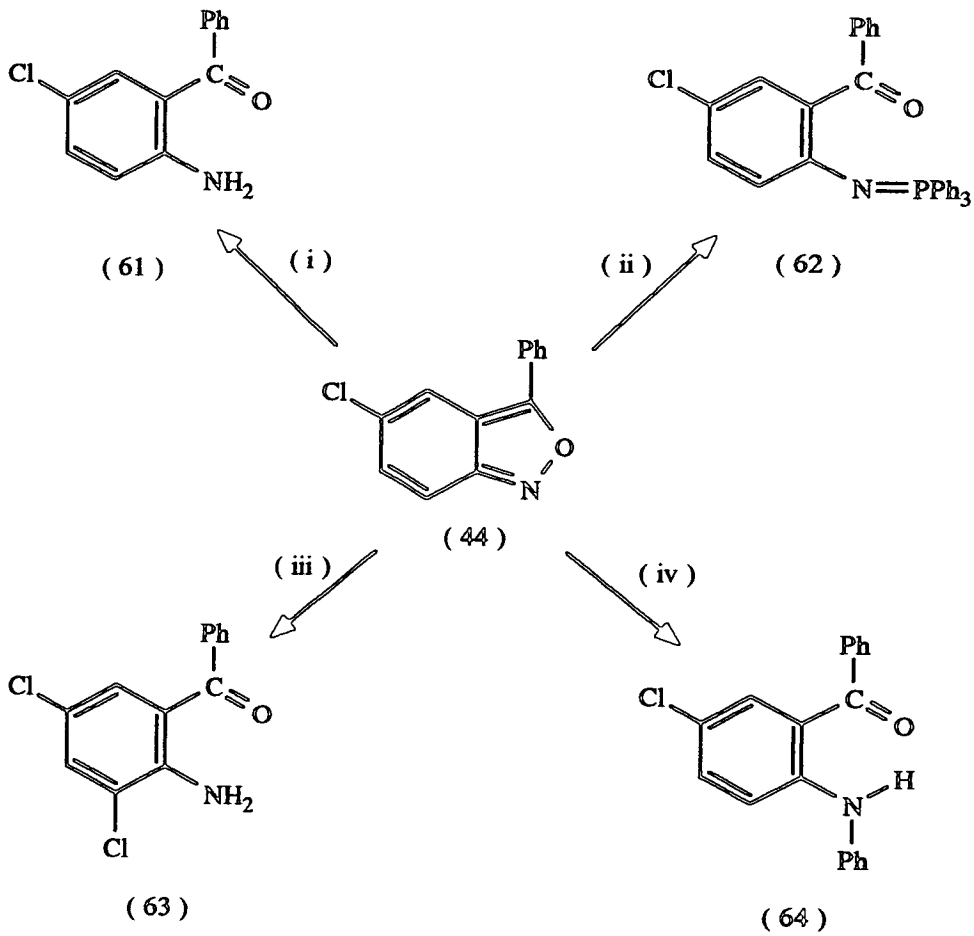
A very interesting sequence of reactions (Scheme 13) result from the thermolysis of 3-azido-2-nitroacetylbenzene (50) to give 3-methyl-7-nitro-2,1-benzisoxazole (54).[21] The authors propose the initial formation of the benzofurazan-N-oxide (51) in this thermal process which exists in equilibrium with tautomer (53), this isomerisation presumably occurring through a 1,2-dinitroso intermediate (52). Tautomer (53) can then undergo cyclisation as shown in Scheme 13 to afford the final 2,1-benzisoxazole product (54).

There are also some diverse reports concerning the synthesis of 2,1-benzisoxazoles from other heterocyclic ring systems, the most controversial of which (Scheme 14) arguably being the acid catalysed isomerisation of isatogens (indol-3-one *N*-oxides), e.g. (55). Much debate occurred over the identity of the rearrangement product until it was proven, by synthesis of this product via an unambiguous route, that the product formed from the acid catalysed rearrangement of 2-phenylisatogen (55) is 3-benzoyl-2,1-benzisoxazole (58).[22] This isomerisation is thought to occur via hydrolytic ring opening of the isatogen (55) forming, via (56), the hydroxylaminoacylbenzene (57) which can then recyclise affording the



(4a) (59) (60)

Scheme 15



(i) H_2, Pd-C, EtOAc, room temp.

(ii) PPh_3, xylene, reflux.

(iii) $SOCl_2$, room temp.

(iv) PhZnCl, $Ni(acac)_2$, THF, room temp.

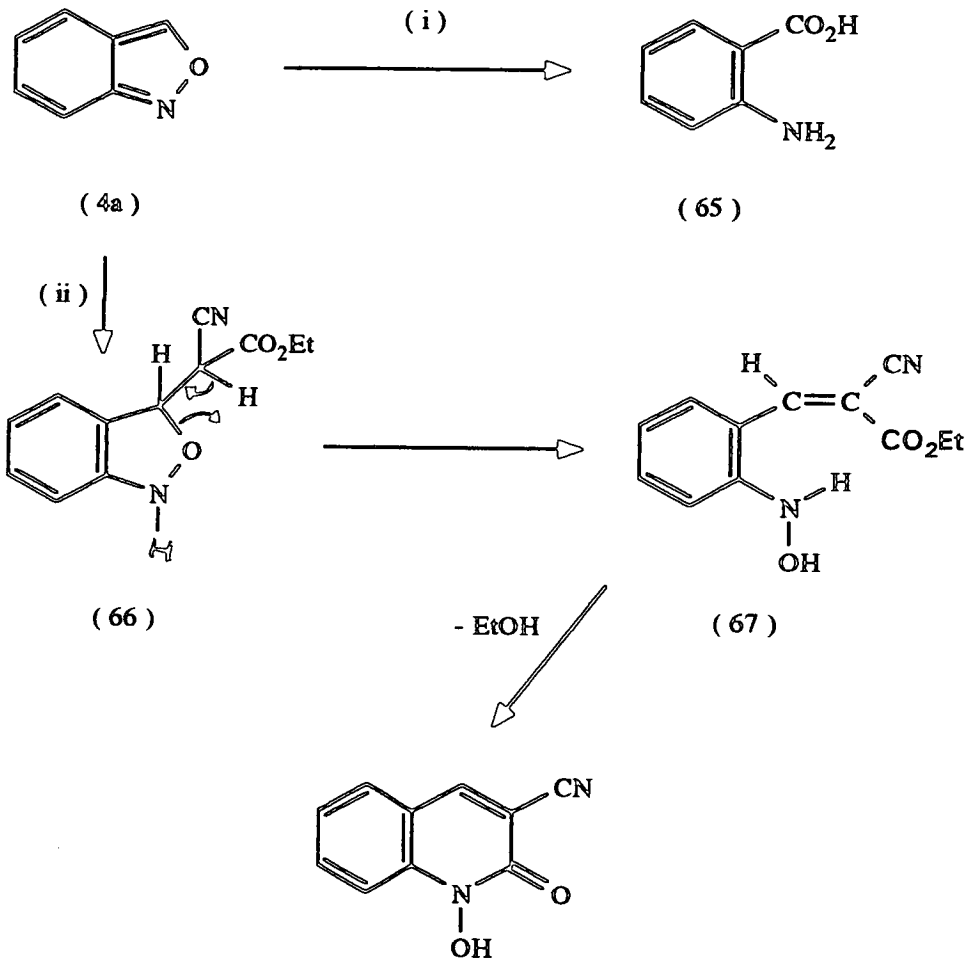
Scheme 16

2,1-benzisoxazole (58) via a process similar to one which has been discussed earlier [see Scheme 1, (2) → (3) → (4)].

1.3 : The Reactivity of Fused 3,4-Isoxazoles

2,1-Benzisoxazole is a 10π heteroaromatic system which can be formally represented (Scheme 15) by the ortho-quininoid structure (4a). However dipole moment measurements show that 2,1-benzisoxazole has considerable polarity (μ = 3.06 D)[23] indicating significant contributions to the ground state of the molecule from canonical forms (59) and (60). Such charge separated structures have important ramifications for the reactivity of fused 3,4-isoxazoles and their derivatives, the outcome of which will become evident in the ensuing discussion.

By far the most important feature in the chemistry of fused 3,4-isoxazoles is the facile fission of the nitrogen to oxygen bond of the isoxazole ring which generates 2-aminoacyl aromatics, a versatile class of synthetic intermediates. The simplest procedure for isoxazole ring scission is via reductive cleavage which can be accomplished by a wide range of common reducing agents. Perhaps the easiest procedure is exemplified (Scheme 16) by the hydrogenation over a palladium catalyst of 5-chloro-3-phenyl-2,1-benzisoxazole (44) to afford 5-chloro-2-aminobenzophenone (61) in near quantitative yield.[24] A multitude of other reagents also induce ring opening of 2,1-benzisoxazoles, some of which are also represented in Scheme 16. Treatment of the 2,1-benzisoxazole (44) with triphenylphosphine affords the phosphiniminobenzophenone (62)[25] while exposure of (44) to thionyl chloride furnishes 2-amino-3,5-dichlorobenzophenone (63),[26] with the unusual introduction of a second chlorine atom into the aromatic ring. Also, a novel and interesting example of the ring opening of 2,1-benzisoxazoles with organozinc reagents has been described,[27] exemplified by the nickel-catalysed reaction of 2,1-benzisoxazole (44) with phenylzinc chloride to give 2-



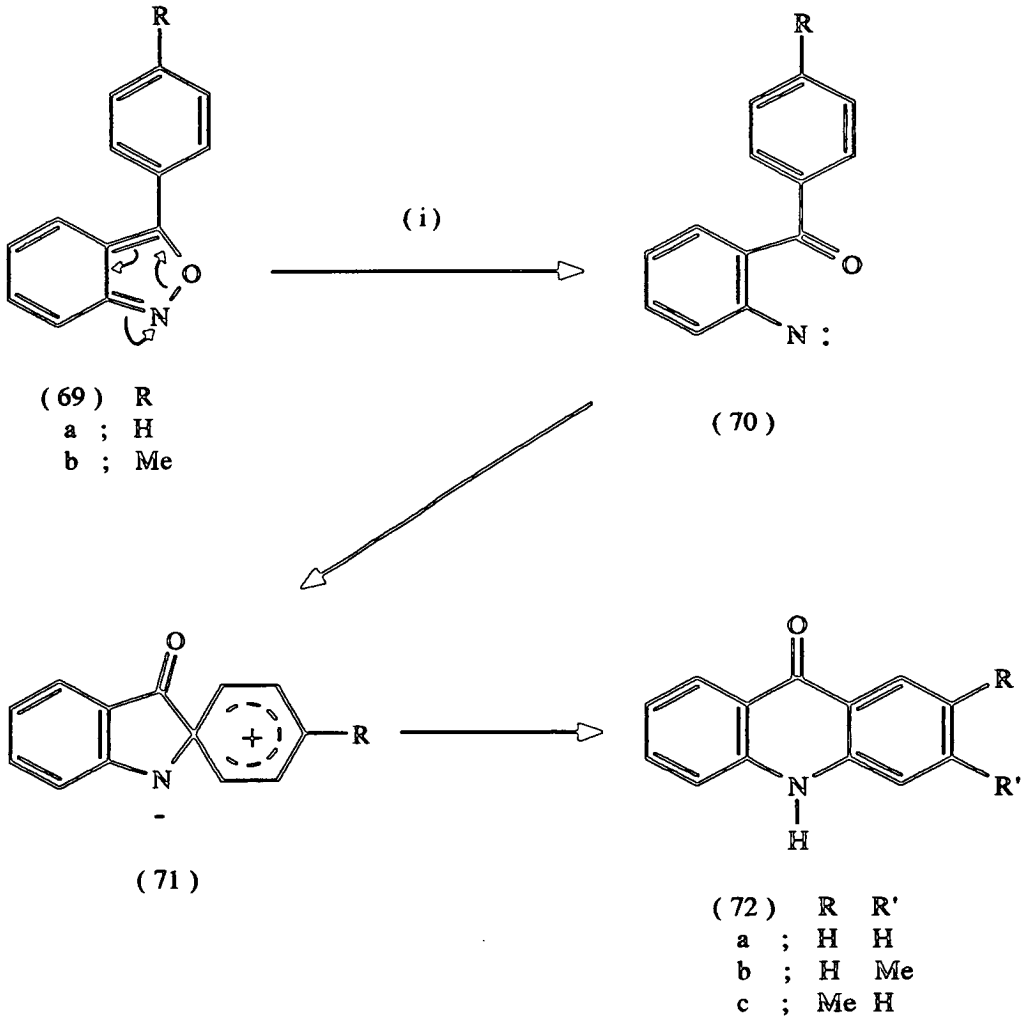
(i) NaOH aqu.
(ii) EtO_2CCH_2CN, piperidine, EtOH.

Scheme 17

phenylaminobenzophenone (64). The 2-aminoacylbenzenes derived by the reduction of 2,1-benzisoxazoles are important synthetic intermediates and a brief account of their synthetic utility will be presented in Chapter 2, Section 2.1 of this thesis.

Fission of the isoxazole ring by alkali (Scheme 17) is one of the oldest known chemical reactions of 2,1-benzisoxazole (4a) resulting in the formation of 2-aminobenzoic acid (anthranilic acid) (65).[28] Carbanions also ring open 2,1-benzisoxazoles and both of these processes are thought to involve nucleophilic attack at the C-3 position. For example, the base catalysed reaction of 2,1-benzisoxazole (4a) with ethyl cyanoacetate affords 3-cyano-1-hydroxyquinol-2-one (68) in excellent yield.[29] This transformation is thought to proceed through nucleophilic attack at C-3 to give an adduct (66) which can rearrange to give the hydroxylamine (67). Subsequent cyclisation of the hydroxylamine (67), with loss of ethanol, then affords the quinolone derivative (68). That nucleophilic substitution reactions occur at the C-3 position of 2,1-benzisoxazoles is not surprising when one takes into account the low electron density (see Scheme 15) at this site.

The interesting thermal rearrangement (Scheme 18) of 3-aryl-2,1-benzisoxazoles (69) to afford acridones (72) has been the subject of substantial investigations.[30,31] The original conjecture to explain the rearrangement of, for example, 3-phenyl-2,1-benzisoxazole (69a) into acridone (72a) was that thermolytic ring opening of the 2,1-benzisoxazole (69) furnishes a nitrene intermediate (70) which can then form the acridone via straightforward nitrene insertion into an aryl C-H bond. However this naive hypothesis must be reviewed in the light of the finding that the pyrolysis, either neat or in a solvent, of 3-(4'-methylphenyl)-2,1-benzisoxazole (69b) yields not only the expected 3-methylacridone (72b) but also 2-methylacridone (72c).[30] The intermediacy of a spiro intermediate (71) has been proposed[31] to explain the concomitant formation of the unexpected rearrangement product.



(69) R
a ; H
b ; Me

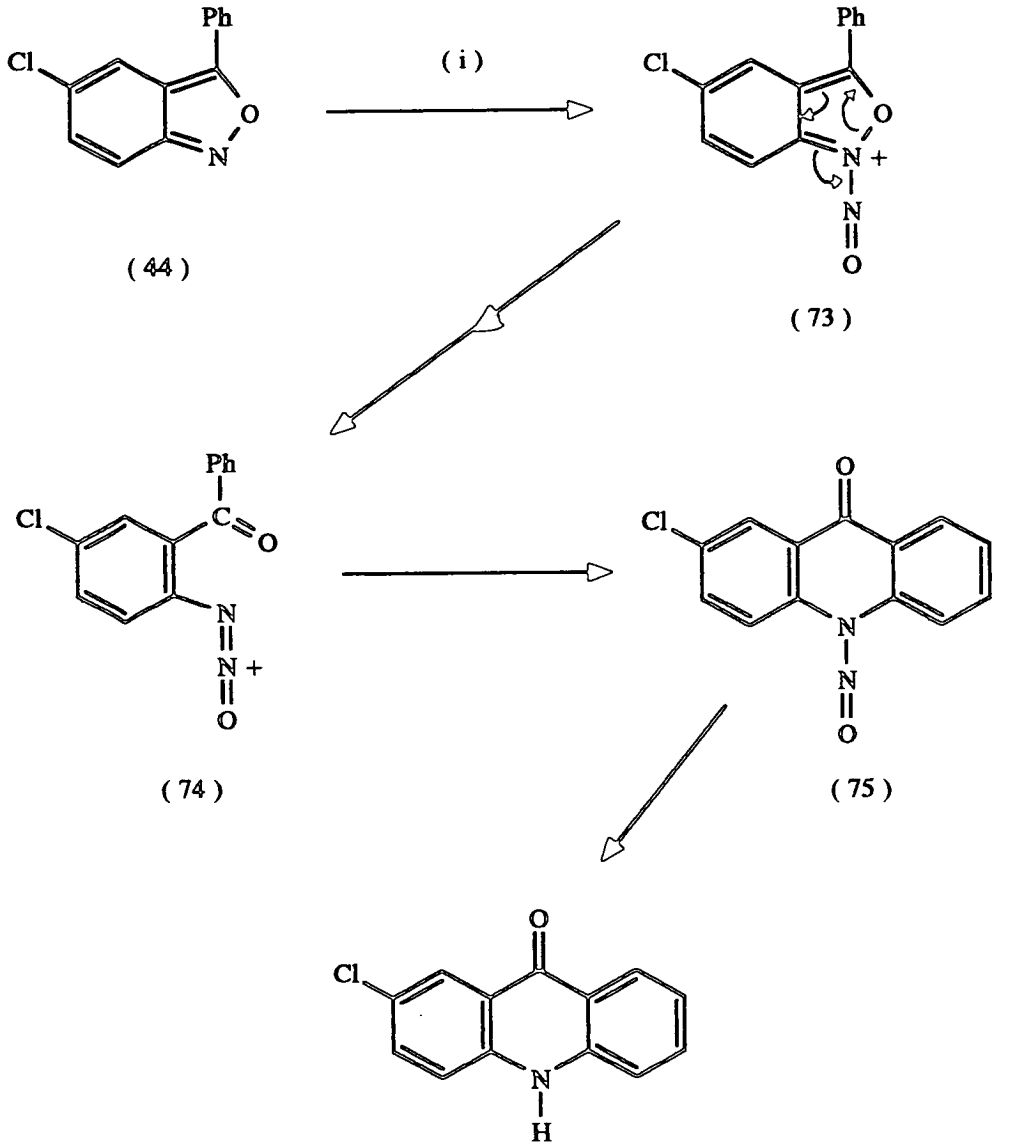
(70)

(71)

(72) R R'
a ; H H
b ; H Me
c ; Me H

(i) heat.

Scheme 18



(44)

(73)

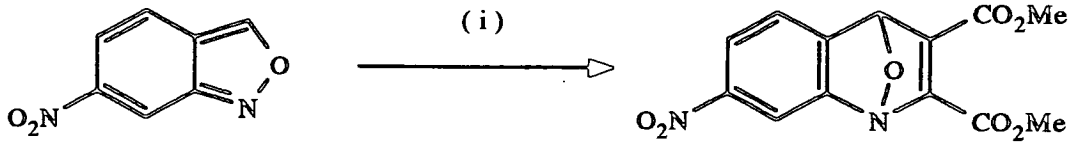
(74)

(75)

(76)

(i) HNO_2.

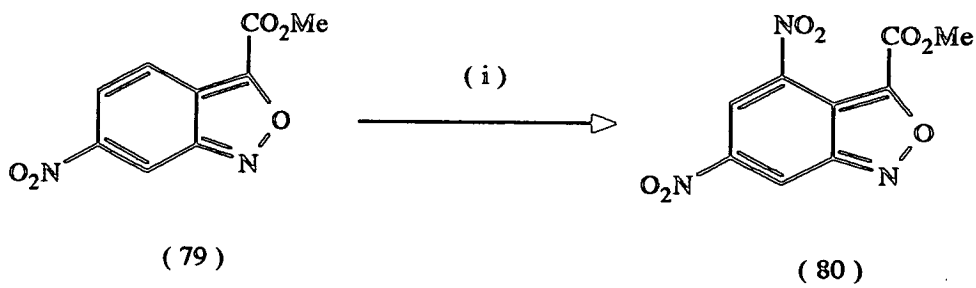
Scheme 19



(77) (78)

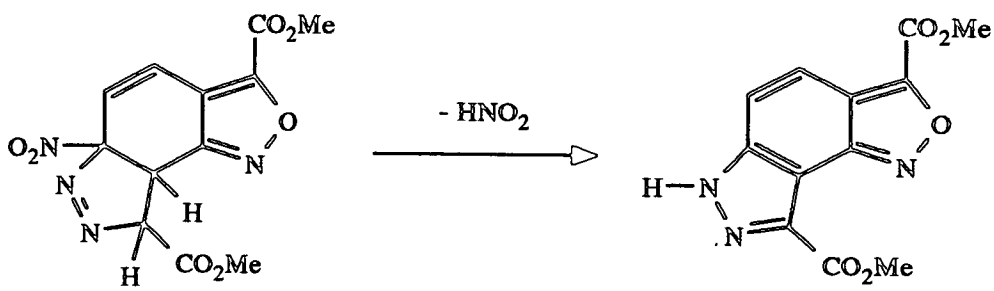
(i) $MeO_2C{\equiv}CO_2Me$, xylene, reflux.

Scheme 20



(79) (80)

(ii)



(81) (82)

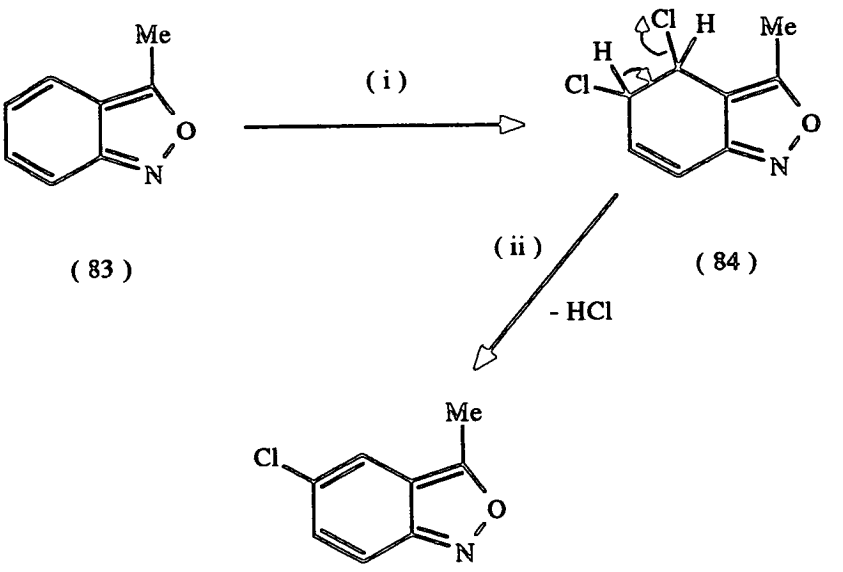
(i) $NaNO_3$, H_2SO_4, 60-65°.

(ii) MeO_2CCHN_2, 100-120°.

Scheme 21

The rearrangement of 3-aryl-2,1-benzisoxazoles into acridones can also be induced by nitrous acid as demonstrated (Scheme 19) by the synthesis of 2-chloroacridone (76) from 5-chloro-3-phenyl-2,1-benzisoxazole (44).[17] It has been proposed that this transformation involves initial nitrosation of the nitrogen atom of the isoxazole ring to afford an intermediate (73)[30] which can rearrange with ring opening to give a species (74), capable of undergoing an intramolecular Friedal-Crafts type reaction to form the acridone nucleus (75). Final hydrolytic cleavage of the N-nitroso compound (73) can then lead to the acridone (76).

The unusual electronic structure of fused 3,4-isoxazoles gives rise to the unique reactivity of these heterocycles reminiscent of both aromatic and olefinic behaviour. For example (Scheme 20), 6-nitro-2,1-benzisoxazole (77) undergoes a Diels-Alder cycloaddition with dimethyl acetylenedicarboxylate to afford the adduct (78),[32] the substrate (77) therefore behaving as a diene. On the other hand (Scheme 21) methyl 6-nitro-2,1-benzisoxazole-3-carboxylate (79) nitrates straightforwardly to furnish methyl 4,6-dinitro-2,1-benzisoxazole-3-carboxylate (80),[32] thereby demonstrating the aromatic character of fused 3,4-isoxazoles. However, the conflicting olefinic nature of methyl 6-nitro-2,1-benzisoxazole-3-carboxylate (79) has also been demonstrated through its participation in a 1,3-dipolar cycloaddition reaction with ethyl diazoacetate to afford the adduct (81), which loses the elements of nitrous acid to finally afford the tricyclic pyrazole derivative (82).[33] Just as intriguing is the behaviour of 2,1-benzisoxazoles towards electrophilic chlorination. As shown in Scheme 22, 3-methyl-2,1-benzisoxazole (83) forms an initial dichloro adduct (84) on treatment with chlorine.[34] Subsequent steam distillation of this fairly volatile adduct results in the elimination of hydrogen chloride to afford 5-chloro-3-methyl-2,1-benzisoxazole (85).



(83)

(84)

(85)

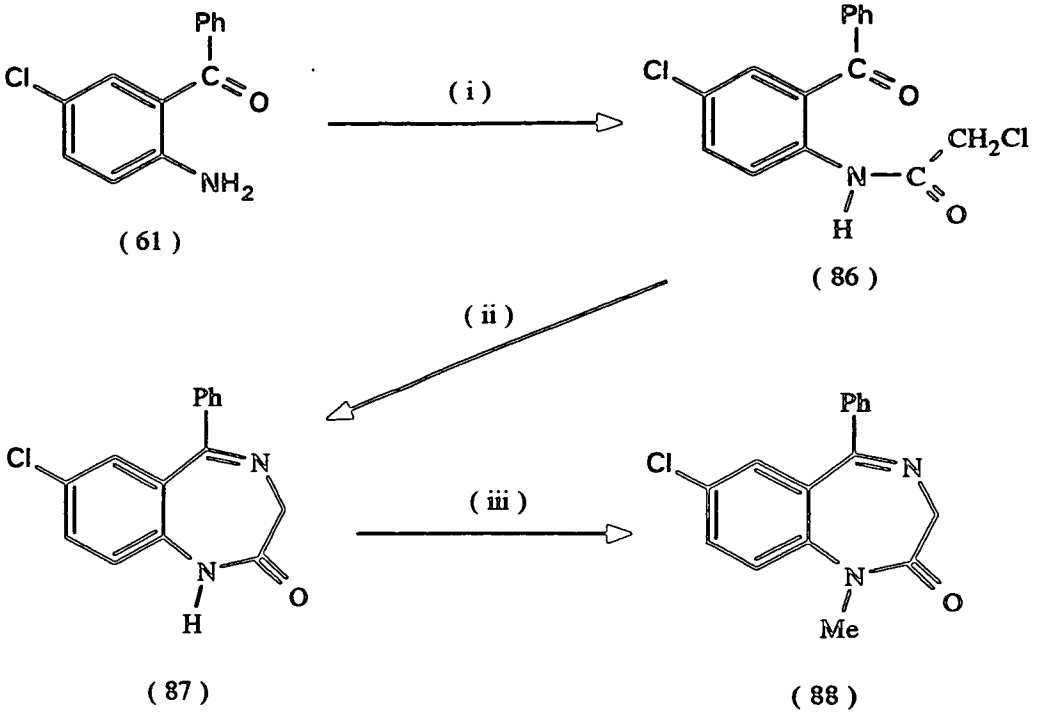
(i) Cl_2, HCl.

(ii) H_2O, reflux.

Scheme 22

Chapter 2

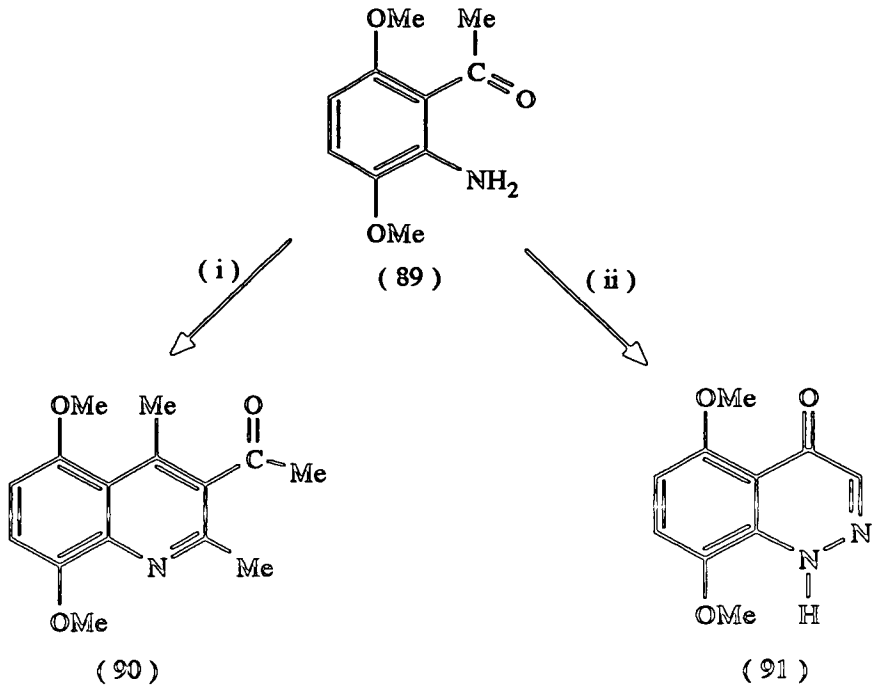
Studies on the Synthesis and Reactivity of Isoxazolopyridine Derivatives



(61) (86) (87) (88)

(i) $ClCH_2COCl$, $CHCl_3$, reflux.
(ii) NH_3, NaI, EtOH, room temp.
(iii) Me_2SO_4, NaOMe, benzene, reflux.

Scheme 23



(89) (90) (91)

(i) $(CH_3CO)_2CH_2$, H_2SO_4, AcOH, reflux.
(ii) $NaNO_2$, HCl, H_2O.

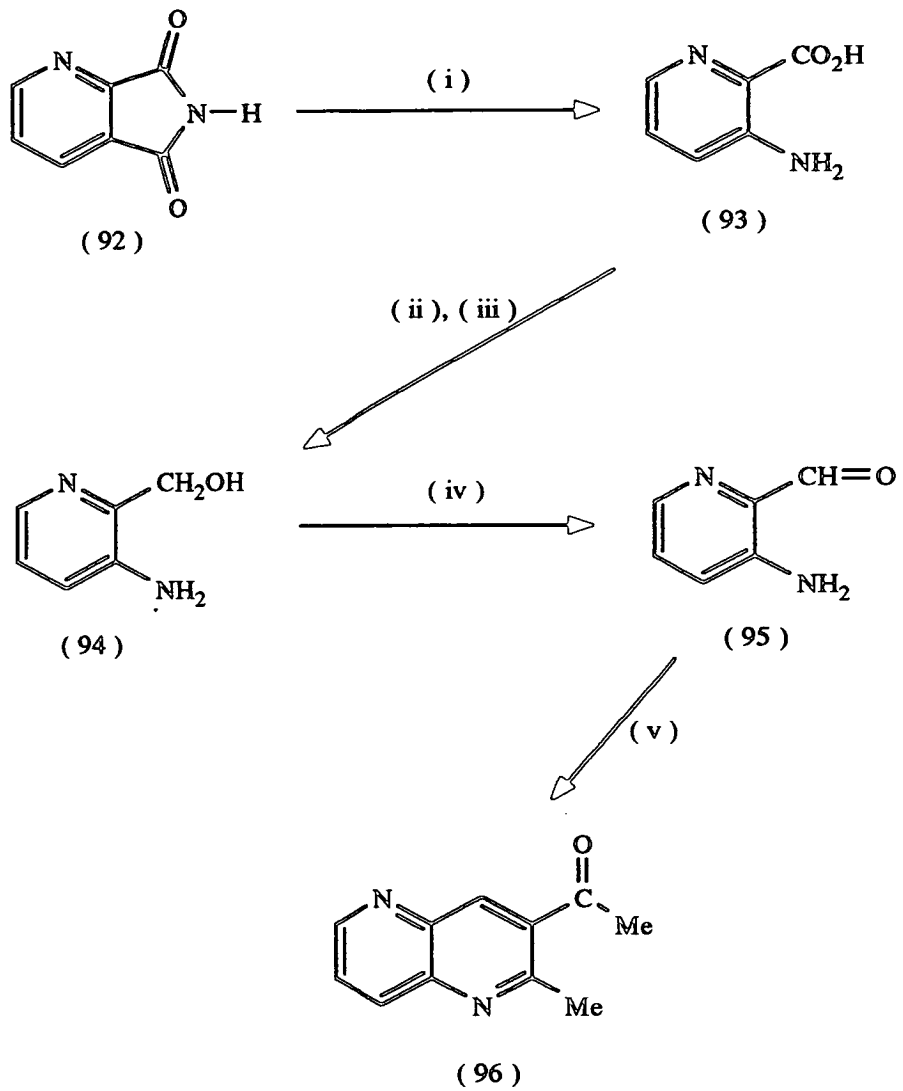
Scheme 24

2 : Studies on the Synthesis and Reactivity of Isoxazolopyridine Derivatives.

2.1 : Introduction

The importance of 2-aminoacyl benzenes in heterocyclic chemistry has been commented on in Chapter 1 of this thesis and synthetic applications of such molecules are widespread. A multitude of benz-fused heterocycles have been prepared from this class of compound, many of which possess important biological activity. For instance, 2-aminobenzophenones have been widely used as precursors to numerous central nervous system drugs of the 1,4-benzodiazepine class[35] exemplified (Scheme 23) by the synthesis of the potent psychotropic agent Diazepam (Valium™) (88) from 2-amino-5-chlorobenzophenone (61).[36] 2-Aminoacyl benzenes are also the precursors of a profusion of other heterocyclic compounds. For example (Scheme 24) the quinoline (90) and the cinnoline (91) derivatives were both synthesised from the same 2-aminoacetophenone precursor (89).[37]

It would be of substantial synthetic importance if such methodologies could be extended to the annulation of 2-aminoacyl heterocycles but no satisfactory route to this latter class of compounds exists to date. A review[38] on the synthesis and annulation reactions of 2-aminobenzaldehydes and 2-amino heteroaromatic aldehydes has been published which highlights the inaccessibility of these heterocyclic systems, many of the published syntheses being multistep processes each being applicable to only a few specific compounds. Synthesis (Scheme 25) of the apparently simple 3-aminopyridine-2-carboxaldehyde (95) for example is far from being trivial and requires quinolinimide (92) as starting material[39] which is firstly converted into the amino acid derivative (93) via Hoffman degradation.[40] Esterification of (93) followed by hydride reduction then affords the alcohol derivative (94) which is finally oxidised to give 3-aminopyridine-2-carboxaldehyde



(i) Br_2, NaOH, room temp.

(ii) H_2SO_4, EtOH, room temp.

(iii) $LiAlH_4$, THF, 5°.

(iv) MnO_2, $CHCl_3$, room temp.

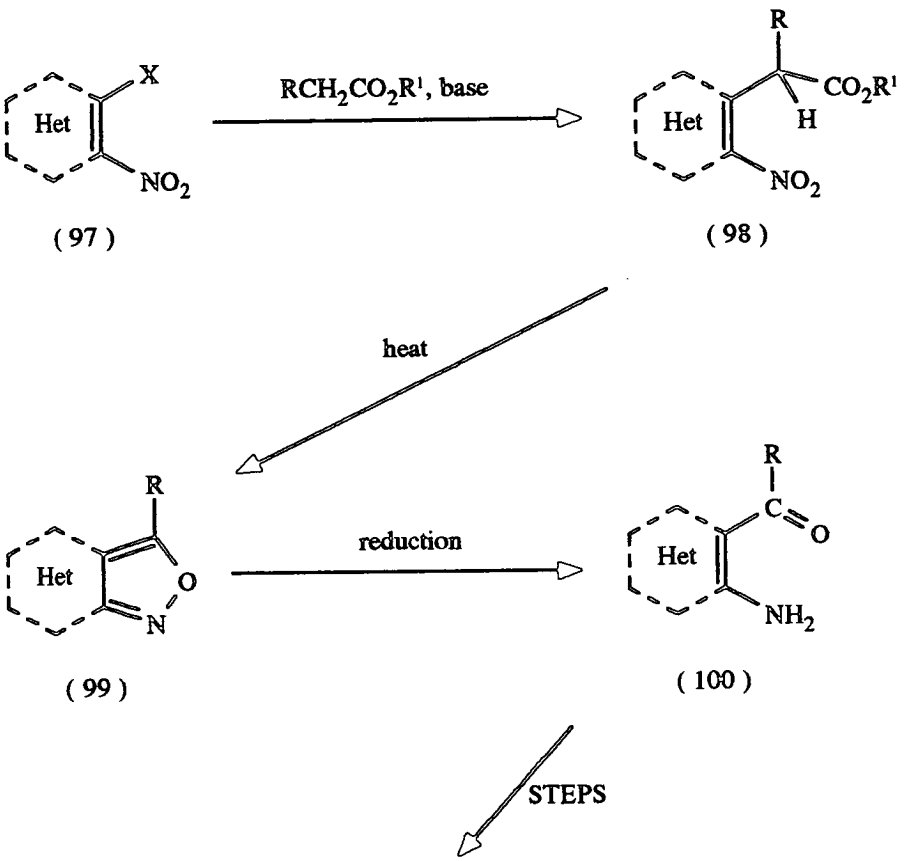
(v) $(CH_3CO)_2CH_2$, heat.

Scheme 25

(95).[41] This amino aldehyde derivative (95) has been used, for instance, in the synthesis of the 1,5-napthyridine derivative (96).[42]

As reported in Chapter 1 of this thesis, 2,1-benzisoxazoles are widely used as precursors of 2-aminoacyl aromatic compounds. A general synthetic approach to heteroaromatic fused 3,4-isoxazoles should therefore provide access to a variety of 2-aminoacyl heterocycles. The development of such an approach was the target at the outset of the present studies and with this in mind of most interest was the aforementioned observation (see Chapter 1; Scheme 9) by Grob and Weissbach[16] that 3-substituted 2,1-benzisoxazoles (39) were formed on heating the 2-nitrophenylacetic acid derivatives (37), which were themselves readily available via the base-catalysed reaction of either diethyl malonate or ethyl cyanoacetate with 2-chloronitrobenzene.[16] Since many 2-halogenonitro heterocycles are commercially available or can be straightforwardly prepared by literature methods, a general approach to the synthesis of heteroaromatic fused 3,4-isoxazoles from these halogenated derivatives was envisaged in the present studies as outlined in Scheme 26. It was postulated that 2-nitro heteroarylacetic acid derivatives (98) should be readily available through the nucleophilic substitution reactions of stabilised carbanions with 2-halogenonitro heteroaromatic compounds (97). The pyrolysis of these acetic acid derivatives (98) should, according to the literature report[16] by Grob and Weissbach, then afford the fused 3,4-isoxazole derivatives (99). Further reduction of these isoxazoles (99) would then afford the hitherto inaccessible 2-aminoacyl heterocycles (100). An attractive feature of this approach is that functionalised 2-aminoacyl heterocycles can be synthesised e.g. [(100) ; R = CO_2R^1, CN, etc] and that this useful functionality can be carried forward and manipulated in the derived fused heterocycles.

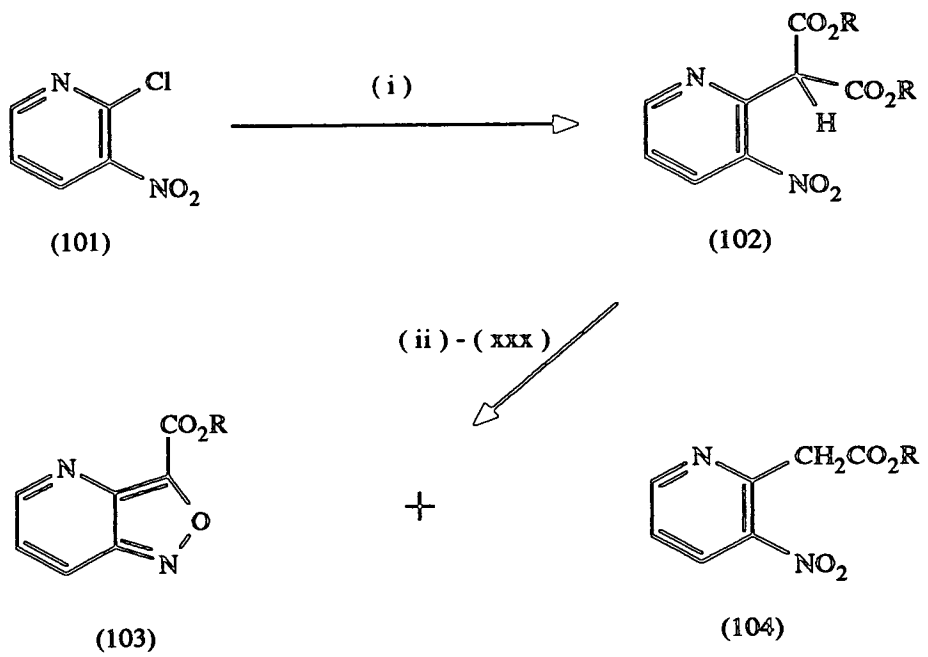
The studies described in this chapter are concerned with the application of the strategy outlined in Scheme 26 to the synthesis of a number of novel isoxazolopyridine derivatives and the exploitation of these in heterocyclic synthesis.



(97) (98) (99) (100)

Het = aromatic or heteroaromatic nucleus.
X = halogen.
R = electron withdrawing group.
R^1 = alkyl or aryl group.

Scheme 26



(i) $CH_2(CO_2R)_2$, NaH, DMF, 100°.
(ii) - (xxx) see Tables 1 and 2.

R
a ; Et
b ; Me
c ; *t*-Bu
d ; CH_2Ph
e ; Na
f ; H

Scheme 27

2.2 : Studies on the Scope of a Novel Isoxazolopyridine Synthesis

An attractive starting point for the present investigations into the proposed synthetic methodology previously outlined in Scheme 26 was the commercially available (Scheme27) 2-chloro-3-nitropyridine (101). The anion of diethyl malonate readily displaced the activated chlorine substituent in (101) to afford the known[43] diethyl 2-(3-nitropyrid-2-yl)malonate (102a) in excellent yield (89%) by a much simpler procedure than those available in the literature.[43] The pyrolysis of this nitropyridylmalonate derivative (102a) was comprehensively investigated during the present studies, the results of which are summarised in Table 1. In an attempt to repeat the observation by Grob and Weissbach[16] in the case of the nitropyridylmalonate (102a), this compound was heated neat at 110-120° under reduced pressure [Table 1; entry (ii)] affording a yellow sublimate which proved however to be only unreacted starting material (102a), no cyclisative decomposition being observed. In refluxing toluene solution [Table 1; entry (iii)] the nitropyridylmalonate (102a) was recovered unchanged even after prolonged heating. However by heating under reflux in the higher boiling solvent xylene [Table 1; entry (iv)] the nitropyridylmalonate (102a) was completely consumed after 48h and an orange, crystalline solid was formed in quantitative yield. The i.r. spectrum of this product showed no absorbtion corresponding to a nitro group, its only assignable feature being a band at 1735 cm^{-1} corresponding to a carbonyl group. The elemental analysis and the remainder of the spectroscopic properties of the orange product are all consistent with it being the desired ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a), which to date is the first known example of this heterocyclic ring system. As further proof of the structure of the isoxazolopyridine (103a) it was hydrolysed with warm aqueous sodium hydroxide to give initially the sodium salt (103e), which itself was fully characterised, and then, by treatment of this salt with aqueous hydrochloric acid, the isoxazolopyridine-3-carboxylic acid derivative (103f).

Table 1 : Pyrolysis Reactions of Diethyl 2-(3-Nitropyrid-2-yl)propanedioate (102a)

Entry	Solvent[a]	Molarity (moles)	Time (h)	Products (% yield)		
				(102a)	(103a)	(104a)
(ii)	none[b]	0.002	0.75	88	-	-
(iii)	toluene	0.002	48	86	-	-
(iv)	xylene	0.002	48	-	100	-
(v)	xylene	0.01	48	3	10	52
(vi)	xylene	0.01	120	[c]	-	-
(vii)	diglyme	0.002	1.5	[d]	-	-
(viii)	DMF	0.002	24	-	8	-
(ix)	pyridine	0.002	32	-	29	-
(x)	collidine	0.005	24	[d]	-	-
(xi)	pyridine[e]	0.005	24	-	-	18
(xii)	pyridine-water	0.01	56	-	-	81
(xiii)	xylene[f]	0.01	24	-	95	-
(xiv)	xylene[g]	0.02	24	-	52	11
(xv)	xylene[h]	0.005	24	-	87	-
(xvi)	xylene[i]	0.005	24	-	26	-
(xvii)	xylene[j]	0.005	24	-	100	-
(xviii)	xylene[j]	0.3	18	-	95	-
(xix)	xylene[k]	0.005	144	-	99[l]	-
(xx)	xylene[m]	0.005	24	-	53	-
(xxi)	xylene	0.005	24	86	-	-
(xxii)	xylene[n]	0.01	5	-	68	-

a, except where noted all reactions were carried out at the reflux temperature of the corresponding solvent ; b, carried out at 110-120° / 0.3mmHg; c, crude product was shown by t.l.c. to contain mainly unreacted starting material (102a); d, gave only an intractable mixture of products; e, with the addition of 0.005mol of powdered NaOH; f, with removal of ethanol by distillation through a 20cm vigreux column; g, with removal of xylene by distillation through a 20cm vigreux column; h, with entrainment of ethanol by a stream of nitrogen gas; i, with cycling of the xylene through a soxhlet extractor containing anhydrous $CaCl_2$; j, with cycling of the xylene through a soxhlet extractor containing anhydrous 5A molecular sieves; k, with anhydrous 5A molecular sieves added to the reaction mixture; l, in a separate run under identical conditions the products and yields obtained were [(103a); 52%] and [(104a); 34%]; m, with cycling of the xylene through an empty soxhlet extractor; n, with the addition of 0.01mol of *para*-benzoquinone.

This high yielding synthesis of the isoxazolopyridine (103a) was very gratifying but on attempting to scale up this heterocyclisation a mixture of products was obtained [Table 1; entry (v)] which were readily separable by flash-chromatography affording only a 10% yield of the desired isoxazolopyridine (103a) along with a second product, an orange oil, whose i.r. spectrum showed that it had retained the nitro group. This oily product was identified as ethyl 2-(3-nitropyrid-2-yl)acetate (104a) on the basis of its elemental analysis and the remainder of its spectroscopic properties. The benzenoid analogue of compound (104a) has been postulated[16] as an intermediate in the synthesis of ethyl 2,1-benzisoxazole-3-carboxylate (39b) by the pyrolysis of diethyl 2-(2-nitrophenyl)malonate (37b) (see Chapter 1; Scheme 9). However a discussion of the origin and fate of this possible intermediate (104a) during the pyrolysis of the nitropyridylmalonate (102a) will be delayed until Chapter 2, Section 2.3 of this thesis as will any discussion concerning the mechanism for the novel transformation [(102) → (103)] which is presently under discussion.

The results for the larger scale pyrolyses of the nitropyridylmalonate (102a) in refluxing xylene solution proved to be variable as shown by the fact that, in one experiment, the prolonged heating of the nitropyridylmalonate (102a) led to the production of a gummy residue which was shown to contain mainly unreacted starting material (102a) [Table 1; entry (vi)]. The failure for the nitropyridylmalonate (102a) to efficiently pyrolyse on a large scale to afford the isoxazolopyridine (103a) was disconcerting and therefore prompted the repetition of the initial, successful small scale pyrolysis of (102a) [Table 1; entry (iv)]. This was found to be completely reproducible therefore alternative conditions for the pyrolysis of the nitropyridylmalonate derivative (102a) were sought which perhaps would be more amenable to larger scale syntheses.

Attempts to induce the thermal cyclisation of the nitropyridylmalonate (102a) by using even higher temperatures gave poor results [Table 1; entries (vii) and

(viii)] with only intractable mixtures being formed on heating the diester (102a) in refluxing diglyme solution while in refluxing dimethylformamide (DMF) solution only a low yield (8%) of the desired isoxazolopyridine (103a) was formed.

It was next anticipated that the thermal cyclisation of the nitropyridylmalonate derivative (102a) might somehow be catalysed by a basic solvent but on heating the diester (102a) under reflux in pyridine [Table 1; entry (ix)] only a 29% yield of the isoxazolopyridine (103a) was isolated. An attempt to improve on this yield by using the higher boiling basic solvent collidine (2,4,6-trimethylpyridine) [Table 1; entry (x)] was made but this led to only complete decomposition of the diester (102a) into intractable mixtures. Under the more strongly basic conditions of powdered sodium hydroxide in pyridine [Table 1; entry (xi)] the only identifiable material that was obtained was the undesired by-product (104a) in low yield. Under the less harshly basic conditions of refluxing aqueous pyridine [Table 1; entry (xii)] the nitropyridylmalonate (102a) afforded a surprisingly high yield (81%) of the nitropyridylacetate derivative (104a). It is believed that under these conditions the nitropyridylmalonate (102a) is undergoing a retro-Claisen type reaction with loss of one ethoxycarbonyl group to afford the monoester (104a).

At this point, it was surmised that the pyrolysis of the nitropyridylmalonate (102a) to afford the isoxazolopyridine (103a) may be an equilibrium process and that driving this equilibrium in the direction of the product (103a) might hopefully improve the reaction. Thus it was postulated that, in the initial steps of the transformation [(102a) → (103a)] ethanol is in some way extruded from the diester (102a) so there is opportunity here to perturb the reaction equilibrium by removing the ethanol so produced. To this end, the nitropyridylmalonate (102a) was heated under reflux in xylene solution using a vigreux column in such a way that any ethanol produced would distil over without distillation of the xylene. This procedure satisfyingly afforded a high yield of the desired isoxazolopyridine (103a) even on a

moderate scale [Table 1; entry (xiii)]. In a slight modification of this procedure the refluxing xylene was co-distilled with the ethanol and replenished when necessary [Table 1; entry (xiv)] but this resulted in a lower yield of the desired product (103a), the more vigorous reflux conditions required presumably leading to some unwanted decomposition of either the starting material or the product. Although good yields of the isoxazolopyridine (103a) were obtained by heating the nitropyridylmalonate (102a) in refluxing xylene with provision for the removal of ethanol as previously described, this approach does suffer from practical difficulties. In particular the relatively long reaction times required for the complete conversion of the diester (102a) into the isoxazolopyridine (103a) made removal of the ethanol by-product difficult in practice. For this reason it was decided to seek a more expedient method for removal of the ethanol by-product and therefore the next method tried was entrainment of the volatile alcohol from the refluxing xylene solution with a stream of nitrogen gas [Table 1; entry (xv)]. This succesfully gave a high yield of the isoxazolopyridine (103a) but it was unfortunately impossible to avoid the simultaneous entrainment of fairly large volumes of xylene therefore giving rise to the risk that the reaction mixture might boil dry. Alternatively, since calcium chloride is known to form stable complexes with ethanol, it was hoped that by cycling of the refluxing xylene through a soxhlet extractor containing anhydrous calcium chloride the ethanol by-product would be efficiently removed. However it was disappointing to find that under these conditions only a 26% yield of the desired isoxazolopyridine (103a) was formed [Table 1; entry (xvi)].

Despite the failure of this approach it was next decided to carry out the pyrolysis of the nitropyridylmalonate (102a) in refluxing xylene with cycling of the solvent through a soxhlet extractor containing 5A molecular sieves, since these have the correct pore size for the inclusion of ethanol. Gratifyingly these conditions afforded [Table 1; entry (xvii)] a quantitative yield of the desired isoxazolopyridine (103a) and most importantly were also amenable to large scale syntheses [Table 1;

Table 2 : Pyrolysis Reactions of 2-(3-Nitropyrid-2-yl)propanedioates (102b-d)[a]

Entry	Substrate	Time (h)	Products (% yield)		
			(102)	(103)	(104)
(xxiii)	(102b)[b]	12	-	100	-
(xxiv)	(102b)[c]	24	-	78	-
(xxv)	(102c)	48	47	11	21
(xxvi)	(102c)[b]	24	-	44	9
(xxvii)	(102c)[c]	24	-	62	-
(xxviii)	(102c)[d]	24	-	50	35
(xxix)	(102d)	24	88	-	-
(xxx)	(102d)	24	94	-	-

a, all reactions were carried out in anhydrous xylene at the reflux temperature (137-144°); b, with removal of the corresponding alcohol by distillation through a 20cm vigreux column; c, with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves; d, with cycling of the solvent through an empty soxhlet extractor.

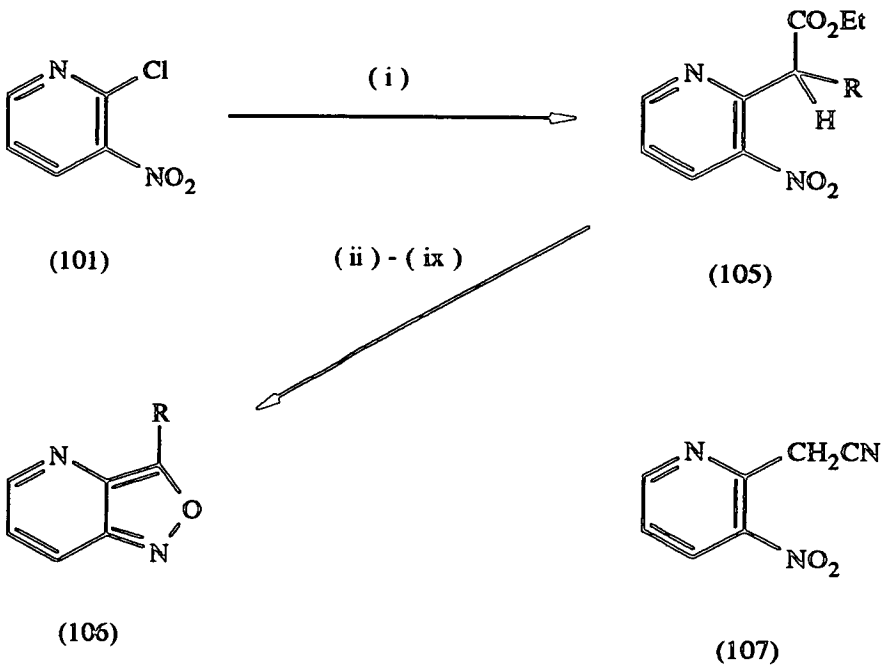
entry (xviii)]. It was next hoped to further simplify these reaction conditions by placing the molecular sieves directly into the reaction vessel during the pyrolysis of the nitropyridylmalonate (102a) however, although in one experiment [Table 1; entry (xix)] an excellent yield of the isoxazolopyridine (103a) was obtained, the time for complete conversion of the diester (102a) into the isoxazolopyridine (103a) was protracted (144h) and the results for different runs of this experiment proved to be variable and irreproducible.

Since the efficient pyrolysis of the nitropyridylmalonate (102a) to afford the isoxazolopyridine (103a) was shown to be crucially dependent on the removal of ethanol from the rection mixture it was also of interest to study the pyrolysis of some esters of nitropyridylmalonates (102) with different alcohol components, the results for which are presented in Table 2. Therefore, the dimethyl malonate derivative (102b) was prepared straightforwardly in 71% yield from 2-chloro-3-nitropyridine (101) and when a xylene solution of (102b) was heated under reflux using a vigreux column in such a way as to remove any extruded methanol an essentially quantitative yield of the isoxazolopyridine methyl ester derivative (103b) was produced [Table 2; entry (xxiii)]. The time required for complete formation of the isoxazolopyridine methyl ester (103b) was approximately half of that required for the analogous ethyl ester (103a) under the same conditions and this may indicate that lower boiling methanol is, as would be expected, more readily removed than ethanol from the reaction mixture by the vigreux column method which was employed. The pyrolysis of the dimethyl ester derivative (103a), using molecular sieves in a soxhlet extractor to remove any methanol by-product, afforded [Table 2; entry (xxiv)] a 78% yield of the isoxazolopyridine (103b). The lower yield of methyl isoxazolo[4,3-b]pyridine-3-carboxylate (103b) obtained compared with that for the ethyl ester (103a) under the identical conditions may be due to tha fact that methanol is not as well absorbed by 5A molecular sieves as ethanol is.

The di-*tert*-butyl malonate derivative (102c) was also readily prepared from 2-chloro-3-nitropyridine (101) in good yield and when heated alone in refluxing xylene solution [Table 2; entry (xxv)] afforded, not unexpectedly, only a low yield (11%) of the desired isoxazolopyridine *tert*-butyl ester (103c) along with some of the *tert*-butyl acetate derivative (104c) (21%) and unreacted starting material (102c) (47%). By removing any extruded *tert*-butanol (b.p. 83°) produced by the fractional distillation procedure described previously, the yield of the isoxazolopyridine *tert*-butyl ester derivative (103c) was increased to 44% [Table 2; entry (xxvi)]. However this reaction also produced was a small amount (9%) of the *tert*-butyl acetate derivative (104c), the rest of the material isolated taking the form of an intractable brown glass. Most surprisingly, the isoxazolopyridine *tert*-butyl ester (103c) was also produced and in good yield (62%) [Table 2; entry (xxvii)] when a xylene solution of the nitropyridylmalonate (102c) was heated under reflux with cycling of the solvent through a soxhlet extractor containing 5A molecular sieves. This result was unexpected since *tert*-butanol was believed to be too bulky to enter into the pores of this type of molecular sieve. This result therfore prompted an investigation of the pyrolysis of the di-*tert*-butyl malonate derivative (102c) in refluxing xylene solution with cycling of the solvent through an empty soxhlet extractor [Table 2; entry (xxviii)]. Under these conditions the yield of the isoxazolopyridine (103c) was still quite high (50%) compared to that found without using the soxhlet extractor [Table 2; entry (xxv)]. This result appears to indicate that the molecular sieves are not necessary for the pyrolysis reaction [(102c) → (103c)] to proceed. In the light of this puzzling result the pyrolysis of the diethyl nitropyridylmalonate derivative (102a) in refluxing xylene solution was re-examined this time with cycling of the solvent through an empty soxhlet extractor [Table 1; entry (xx)]. These condition did indeed afford the isoxazolopyridine ethyl ester (103a) but in only moderate yield (53%). The pyrolysis reactions of the nitropyridylmalonates (102a-c) using the soxhlet extractor procedures were performed in larger volumes of solvent than

under the straight reflux-only conditions to take into account the volume of solvent temporarily retained in the soxhlet extractor. Therefore it was thought that the effect of lowering the concentration of the reaction mixture could be the reason for the improved yields of cyclised products obtained when carrying out the pyrolysis of the nitropyridylmalonates (102a-c) using a soxhlet extractor. However when a xylene solution of the diethyl nitropyridylmalonate (102a) was heated under vigorous reflux in the same volume of xylene as was used during the empty soxhlet extractor experiment only a high yield of recovered starting material was obtained, even after prolonged heating [Table 1; entry (xxi)]. A potential explanation for these anomalous results is that during the pyrolysis of the nitropyridylmalonates (102a) and (102c) in refluxing xylene solution with cycling of the solvent through an empty soxhlet extractor, the extruded alcohol is temporarily resident in the soxhlet extractor before being siphoned back into the reaction mixture. This therefore upsets the reaction equilibrium. As the removal of the alcohol is not permanent, as it should be when utilising molecular sieves, then this may account for the poorer yield of product obtained in this case. The isolated yields of the isoxazolopyridine *tert*-butyl ester (103c) from the pyrolysis of the diester (102c) with cycling of the solvent through a soxhlet extractor either with or without molecular sieves are within reasonable experimental error (62% and 50% respectively) on the scales on which the reactionswere performed and this may indicate that for this reaction [(102c) → (103c)] the molecular sieves are playing no part in the removal of *tert*-butanol.

The dibenzyl malonate derivative (102d) was also prepared from 2-chloro-3-nitropyridine (101) in high yield (94%) for the purpose of studying the pyrolysis of a malonic ester of an involatile alcohol. Not surprisingly, it was found that the dibenzyl malonate derivative (102d) was recovered unchanged in high yield after heating under reflux in xylene solution for 24h [Table 2; entry (xxix)]. The pyrolysis of (102d) was next attempted in refluxing xylene solution with cycling of



(i) EtO_2CCH_2R, NaH, DMF, 100°.
(ii) to (ix) see Table 3.

R

a ; COMe
b ; COPh
c ; $COCH_2CO_2Et$
d ; CN
e ; SO_2Ph

Scheme 28

the solvent through a soxhlet extractor containing 5A molecular sieves. This reaction was investigated not because it was wrongly hoped that the molecular sieves would absorb any extruded benzyl alcohol but to acertain as to whether the sieves were having some unrealised catalytic effect such as reactions occuring on the surface of small particles of sieve which may have been washed into the reaction mixture by the hot solvent. However, under these conditions [Table 2; entry (xxx)] only a high yield of unreacted starting material (102d) was isolated. The failure of the dibenzyl malonate derivative (102d) to undergo pyrolysis was not unexpected since there was no route provided for the removal of the involatile benzyl alcohol (b.p. 205^0) necessary for successful pyrolysis to occur.

All of the experimental evidence obtained at this point indicates that for the thermal cyclisation of the dialkyl malonate derivatives (102a-c) to afford isoxazolopyridines (103a-c) to proceed efficiently then provision must be made for the removal of the corresponding alcohol portion of the malonate. With this proviso in mind it was next decided to try and extend this new isoxazolopyridine synthesis (Scheme 28) to the pyrolysis of a number of 2-substituted (3-nitropyrid-2-yl)acetate derivatives (105). First to be studied was the β-ketoester derivative (105a) which was prepared in 62% yield by the reaction of 2-chloro-3-nitropyridine (101) with ethyl acetoacetate. The ^{1}H n.m.r. and ^{13}C n.m.r. spectra of this orange oil (105a) in deuterochloroform showed it to exist as a complex mixture of at least three different tautomers. The exact assignment of each of these tautomers was not possible from the given spectroscopic data. However the tendency for β-ketoesters to tautomerise is a well known feature of this type of compound so this matter was not pursued any further.

The pyrolysis of the β-ketoester (105a) in refluxing xylene solution using molecular sieves to remove ethanol as described previously afforded [Table 3; entry (ii)], along with some unreacted starting material (105a), only a disappointingly low yield (8%) of an orange solid the structure of which was only tentatively assigned as

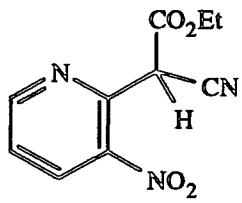
Table 3 : Pyrolysis Reactions of Ethyl 2-(3-Nitropyrid-2-yl)ethanoates (105a, b, d and e)

Entry	Substrate	Solvent[a]	Molarity (moles)	Time (h)	Product	(% yield)
(ii)	(105a)	xylene	0.004	48	(106a)[b]	8
(iii)	(105b)	xylene	0.004	28	(106b)	23
(iv)	(105b)	pyridine-water	0.01	48	(104a)	69
(v)	(105d)	xylene	0.002	48	(106d)	69
(vi)	(105d)	xylene	0.01	120	(106d)	14
(vii)	(105d)	xylene[c]	0.025	48	(106d)	83
(viii)	(105d)	pyridine-water	0.01	10	(107)	36
(ix)	(105e)	xylene[c]	0.0035	72	[d]	-

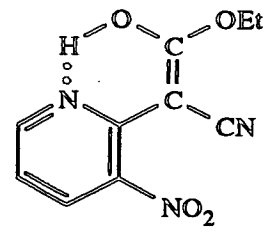
a, all reactions were carried out at the reflux temperature of the corresponding solvent; b, also isolated was some unreacted starting material [(105a); 36%]; c, with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves; d, gave only an intractable mixture of products.

the expected 3-acetylisoxazolo[4,3-b]pyridine (106a) on the basis of its i.r. spectrum and mass spectroscopic data. As a result of this poor yield insufficient quantities of (106a) were available to rigorously characterise this compound. The ethyl benzoylacetate derivative (105b) was next prepared in 68% yield from 2-chloro-3-nitropyridine (101) and in contrast to the ethyl acetoacetate derivative (105a) its ^1H n.m.r spectrum in deuterochloroform showed it to exist as predominately one tautomer in this solvent. The pyrolysis of the ethyl benzoylacetate derivative (105b) was performed in refluxing xylene solution using molecular sieves to remove the ethanol by-product but these conditions also gave a disappointingly low yield (23%) of the desired isoxazolopyridine derivative (106b). Since the benzoylacetate derivative (105b) was in hand it was considered of interest to also investigate its pyrolysis in refluxing aqueous pyridine solution, a solvent medium which was shown to promote the removal of an ethoxycarbonyl substituent from a structurally similar pyridine derivative [see Table 1; entry (xii)]. However, under these conditions [Table 3; entry (iv)] it was found that selective cleavage of the benzoyl group occurs from (105b) to give ethyl 2-(3-nitropyrid-2-yl)acetate (104a) in good yield (69%).

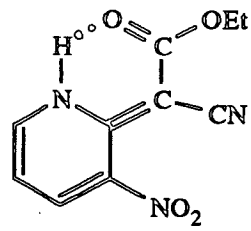
Despite the disappointing results obtained in the attempted pyrolyses of the β-ketoesters (105a) and (105b) an attempt was made to prepare the β-ketoester derivative (105c) via the base catalysed reaction of 2-chloro-3-nitropyridine (101) with diethyl acetonedicarboxylate in order to hopefully study its pyrolysis. However, under the standard conditions employed for the condensation reactions of stabilised carbanions with 2-halogenonitro heterocycles (sodium hydyride in DMF at 100°) only a high yield (91%) of ethyl 2-(3-nitropyrid-2-yl)acetate (104a) was obtained. Presumably this product arises from the desired β-ketoester derivative (105c) by further base-catalysed cleavage of the acetonedicarboxylate side chain. In an attempt to suppress this cleavage reaction the condensation of 2-chloro-3-nitropyridine (101) with the anion of diethyl acetonedicarboxylate was attempted at



(105d)



(108)



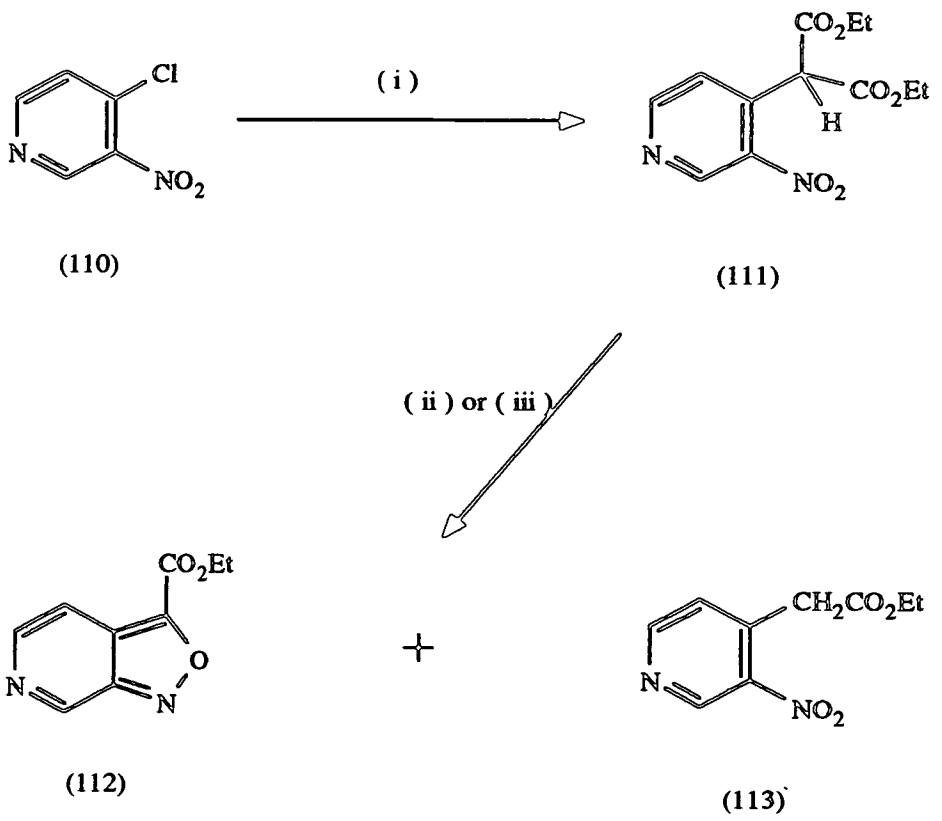
(109)

Scheme 29

lower temperatures. However, by conducting this reaction at either room temperature or at 50° only a high recovery of both unreacted starting materials was obtained in both cases and so it was decided to abandon attempts to synthesise the β-ketoester derivative (105c).

2-Chloro-3-nitropyridine (101) also reacted readily with the anion of ethyl cyanoacetate to afford the known[44] cyanoacetate derivative (105d) in excellent yield as a bright orange solid. The ^{1}H n.m.r. spectrum in deuterochloroform and the ^{1}H and ^{13}C n.m.r spectra in hexadeuterio dimethylsulphoxide of the cyanoacetate derivative (105d) show that it exists in these solvents as two tautomeric forms in the approximate ratio of 4 : 1. The precise structural assignment of these two tautomers is not possible even with all of the availiable data as the signals for the minor tautomer are too weak to unequivocally assign. However (Scheme 29), the enol structure (108) has been previously reported[44] as the main tautomeric form for the cyanoester (105d) this assignment being based primarily on data from i.r. spectroscopy. The n.m.r data obtained during the present studies is not inconsistent with the major tautomer having structure (108). However other forms such as (105d) and (109) cannot be completely ruled out but any further investigations on the tautomeric behaviour of the nitropyridylcyanoacetate (105) were not deemed worthwhile.

The pyrolysis of the cyanoacetate (105d) was firstly performed on a small scale in refluxing xylene solution [Table 3; entry (v)] and did indeed afford the desired 3-cyanoisoxazolo[4,3-b]pyridine (106d) in good yield (69%). However, as expected from previous results, this pyrolysis could not be efficiently carried out on a larger scale, where only a low yield of the desired product (106d) was obtained [Table 3; entry (vi)]. When provision is made for the removal of the ethanol by-product by application of the previously described molecular sieve protocol, the large scale pyrolysis of the cyanoacetate (105d) affords an excellent yield (83%) of the desired isoxazolopyridine (106d) [Table 3; entry (vii)]. As an aside, the



(110)

(111)

(112)

(113)

(i) $CH_2(CO_2Et)_2$, NaH, DMF. 100°.
(ii) xylene, mol. sieves 5A, reflux.
(iii) pyridine, H_2O, reflux.

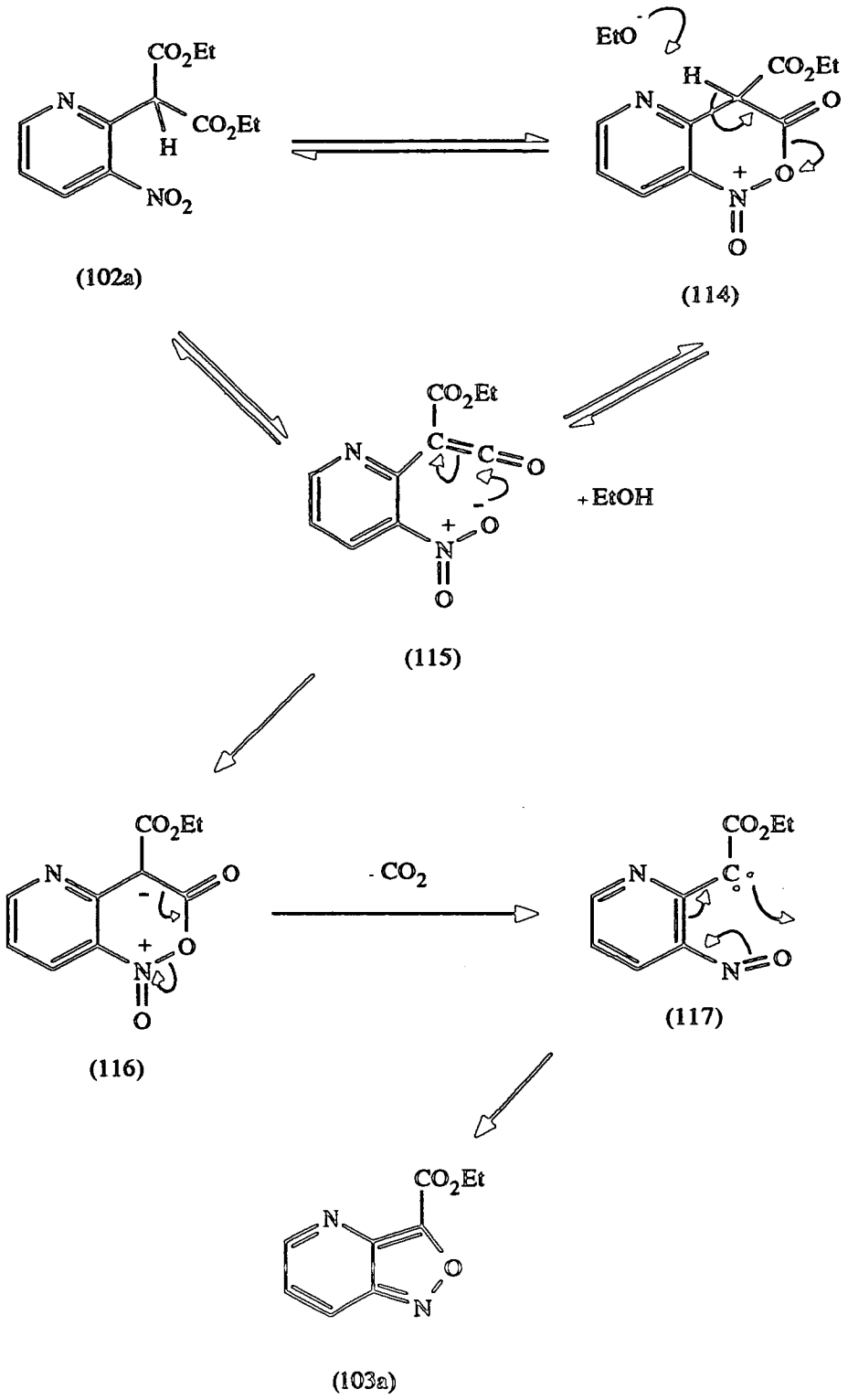
Scheme 30

pyrolysis of the cyanoacetate (105d) was also examined in aqueous pyridine solution [Table 3; entry (viii)] and under these conditions the ethoxycarbonyl group of (105d) was removed as anticipated to afford the known[45] acetonitrile derivative (107) albeit in low yield (36%).

The next nitropyridylacetate derivative whose pyrolysis was of interest to study was the benzenesulphonyl derivative (105e). 2-Chloro-3-nitropyridine (101) was treated with the anion of ethyl benzenesulphonylacetate and gave the desired product (105e) but in only 26% yield, the only other identifiable material isolated from this reaction being some benzenesulphonylacetic acid. The pyrolysis of (105e) in refluxing xylene using molecular sieves in a soxhlet extractor to remove the ethanol by-product proved to be very disappointing [Table 3; entry (ix)]. These conditions resulted in only the formation of a dark, intractable mixture of products from which no identifiable material could be obtained. Therefore further studies on the preparation and pyrolysis of (105e) were not undertaken. The foregoing results obtained in the attempted pyrolysis of the 2-substituted (3-nitropyrid-2-yl)acetate derivatives (105a-e) were very discouraging, except for the cyanoacetate derivative (105d), and therefore further investigations on the pyrolysis of this type of compound were discontinued at this point.

It was next desired to extend the scope of the pyrolysis reaction presently under investigation to include (Scheme 30) the 3-nitropyrid-4-yl malonate derivative (111). 4-Chloro-3-nitropyridine was readily prepared by a literature procedure[46] and was subsequently treated with the anion of diethyl malonate to afford the known[47] diethyl 2-(3-nitropyrid-4-yl)malonate (111) in excellent yield (97%). The pyrolysis of the nitropyridylmalonate (111) in refluxing xylene solution using molecular sieves to remove the ethanol by-product gratifyingly resulted in the production of the desired isoxazolo[3,4-c]pyridine derivative (112) in good yield (69%), this being the first known synthesis to date of this heterocyclic ring system. Also isolated from this pyrolysis reaction was a small amount (7%) of the

nitropyridylacetate derivative (113) which itself could be independently prepared in good yield (73%) by heating the diester (111) under reflux in aqueous pyridine. The isoxazolopyridine (112) was isolated in pure form by flash chromatography of the crude pyrolysis mixture and formed yellow needles whose elemental analysis and spectroscopic properties were all in accord with the assigned strucure. However attempted large scale purification of the isoxazolopyridine (112) by flash chromatography resulted in total decomposition of the product giving intractable black tars. The reason for this behaviour on a large scale still remains unclear and therefore it was necessary to use the crude isoxazolopyridine (112) in further reactions (see Chapter 2, Section 2.5) followed by purification of the subsequent reaction products.

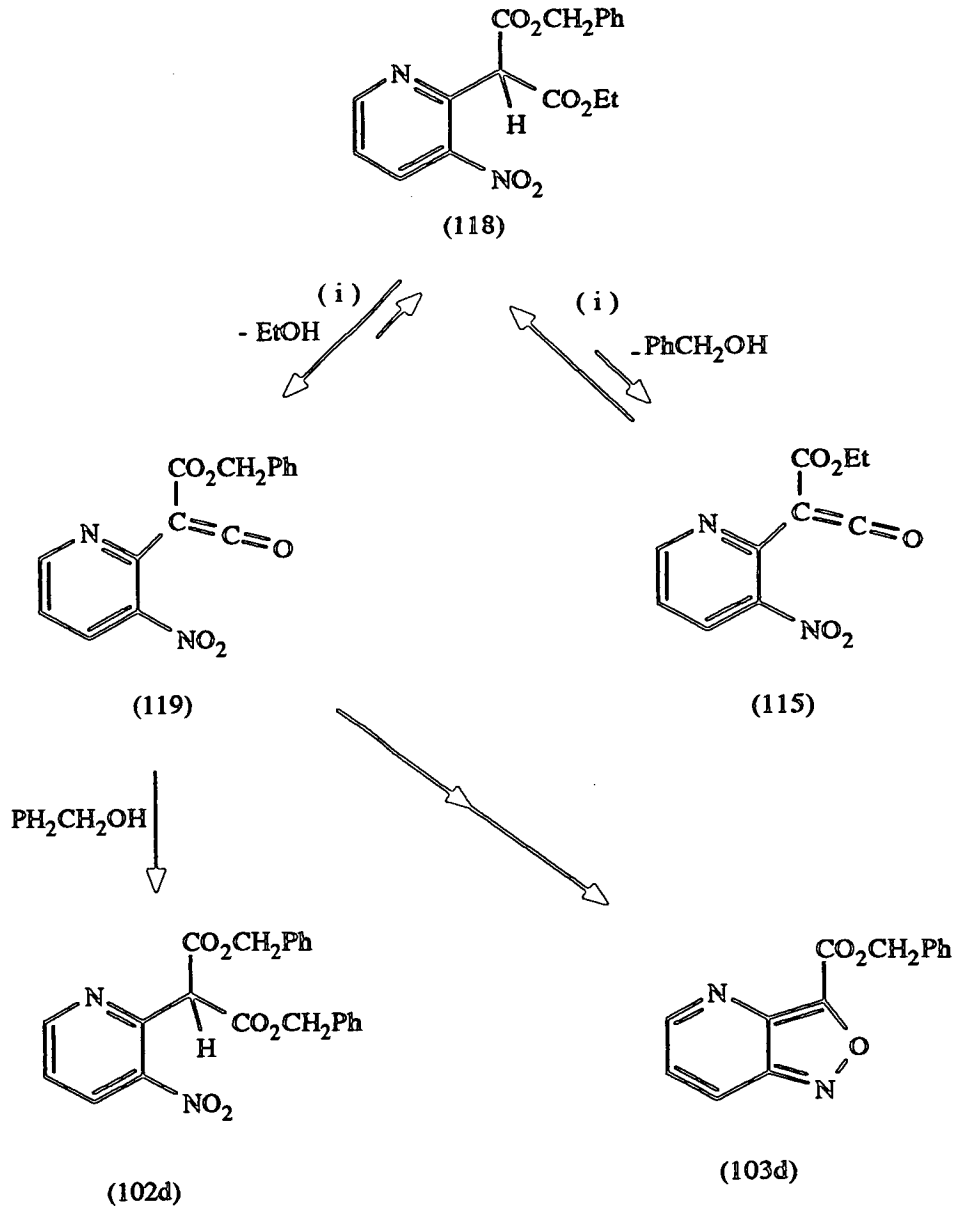

CO2Et
CO2Et
H
NO2
N
(102a)
EtO
H
CO2Et
O
O
N
O
(114)
CO2Et
C
C
O
N
O
N
O
+EtOH
(115)
CO2Et
O
N
O
N
O
(116)
-CO2
CO2Et
C
N
O
(117)
CO2Et
N
O
N
(103a)

Scheme 31

2.3 : Studies on the Mechanism of the Isoxazolopyridine Synthesis

Having studied the scope of the isoxazolopyridine synthesis in the previous section attention was next turned to the investigation of the mechanism of this interesting transformation. It has been previously proposed by Grob and Weissbach[16] (see Chapter 1; Scheme 9) that the 2-nitrobenzyl derivatives (38) are intermediates in the thermal conversion of the 2-nitrophenylacetates (37) into the 3-substituted 2,1-benzisoxazoles (39). This conjecture was examined for the isoxazolopyridine synthesis under investigation in the present studies by the heating of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) under reflux in xylene for 48h. Under these conditions diethyl 2-(3-nitropyrid-2-yl)malonate (102a) is converted quantitatively into the isoxazolopyridine derivative (103a) (see Section 2.2). However only a quantitative yield of unreacted nitropyridylacetate (104a) was recovered under these conditions and therefore the intermediacy of the monoester (104a) in the transformation [(102a) $\Rightarrow$ (103a)] is unlikely.

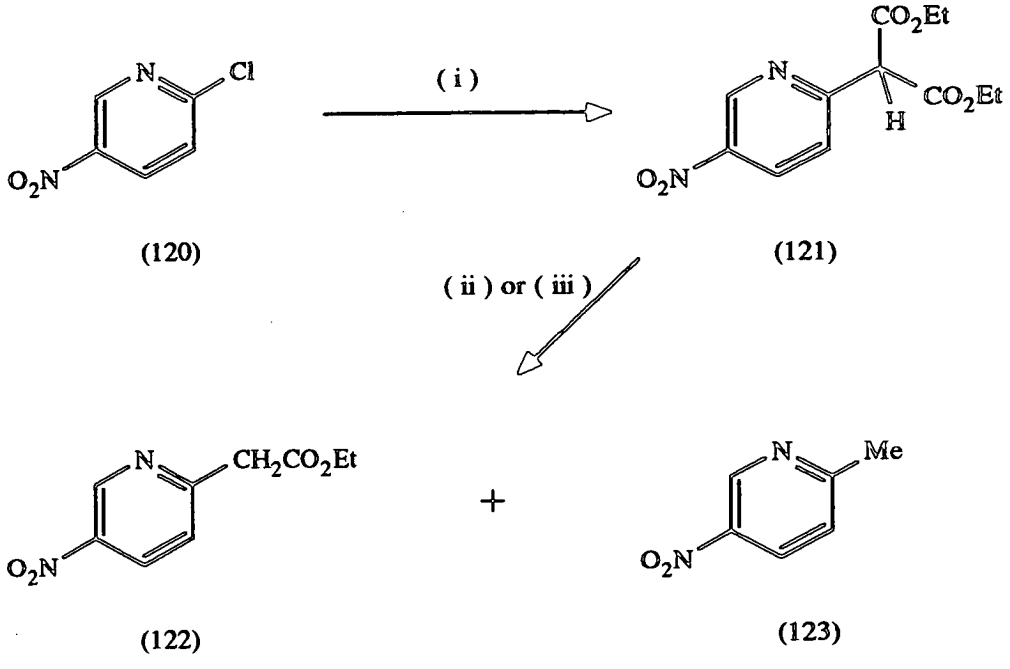
A plausible mechanism for the thermal synthesis of fused 3,4-isoxazoles from 2-nitroaryl and 2-nitro heteroarylacetate derivatives is is outlined in Scheme 31 for the synthesis of the isoxazolopyridine (103a). It is postulated that the first step in the mechanism for this transformation is an equilibrium process involving the thermal loss of ethanol from the diester (102a) to afford, either directly or through participation of the nitro group via the bicyclic intermediate (114), the ketene derivative (115). The pyrolysis of substituted and unsubstituted malonate derivatives is known[48] to afford ketenes through the thermal loss of an alcohol. Further interaction of the *ortho*-nitro group with the adjacent ketene functionality in the intermediate (115) can then afford the bicyclic, zwitterionic intermediate (116). Loss of carbon dioxide from this transient species can then furnish the 2-nitrosoaryl carbene intermediate (117) which, via a six electron electrocyclisation process can then afford the final isoxazolopyridine product (103a). This postulated mechanism is analogous to that proposed by Prokipcak[49] for



(i) xylene, mol. sieves 5A, reflux.

Scheme 32

the thermal conversion of 2-nitrophenyl carbamate derivatives into benzofurazans. This process is believed to involve 2-nitroaryl isocyanate and 2-nitrosoaryl nitrene intermediates equivalent to the currently proposed ketene (115) and carbene (117) species respectively. This mechanistic rationale outlined in Scheme 31 can also account for the formation of the nitropyridylacetate by-product (104a) during the pyrolysis of the nitropyridylmalonate (102a) by either of two possible routes both derived from the proposed ketene intermediate (115). Reaction of the ketene (115) with any trace amounts of water would give an ethyl hydrogen malonate derivative which will then readily decarboxylate to give the monoester by-product (104a). Alternatively the ketene (115) may undergo thermal decarbonylation to give a carbene intermediate which, after some unspecified hydrogen abstraction process, can also yield the monoester (104a). The former explanation for the formation of the monoester (104a) is favoured since the latter type of process normally requires much higher temperatures[50] than those encountered in the present work but some contribution from the latter process cannot be excluded. Circumstantial evidence for the intermediacy of a ketene in the thermal cyclisation reaction presently under discussion was obtained (Scheme 32) from the pyrolysis of the mixed dialkyl malonate derivative (118), which was itself readily prepared by the reaction of benzyl ethyl malonate with 2-chloro-3-nitropyridine (101). The pyrolysis of the diester (118) in refluxing xylene solution with the removal of the ethanol by-product by molecular sieves afforded, along with a moderate yield (53%) of the anticipated isoxazolopyridine benzyl ester (103d), a 13% yield of the unanticipated dibenzyl malonate derivative (102d). This result may be explained in the following manner. When heated in refluxing xylene the benzyl ethyl malonate derivative (118) exists in equilibrium with two possible ketene intermediates (115) and (119). Since ethanol is being removed by the molecular sieves then this equilibrium is driven towards the benzyloxycarbonyl ketene (119) which, by a process similar to that shown in Scheme 31, can subsequently afford the isoxazolopyridine benzyl ester (103d). Alternatively, addition of benzyl alcohol to the ketene (119)



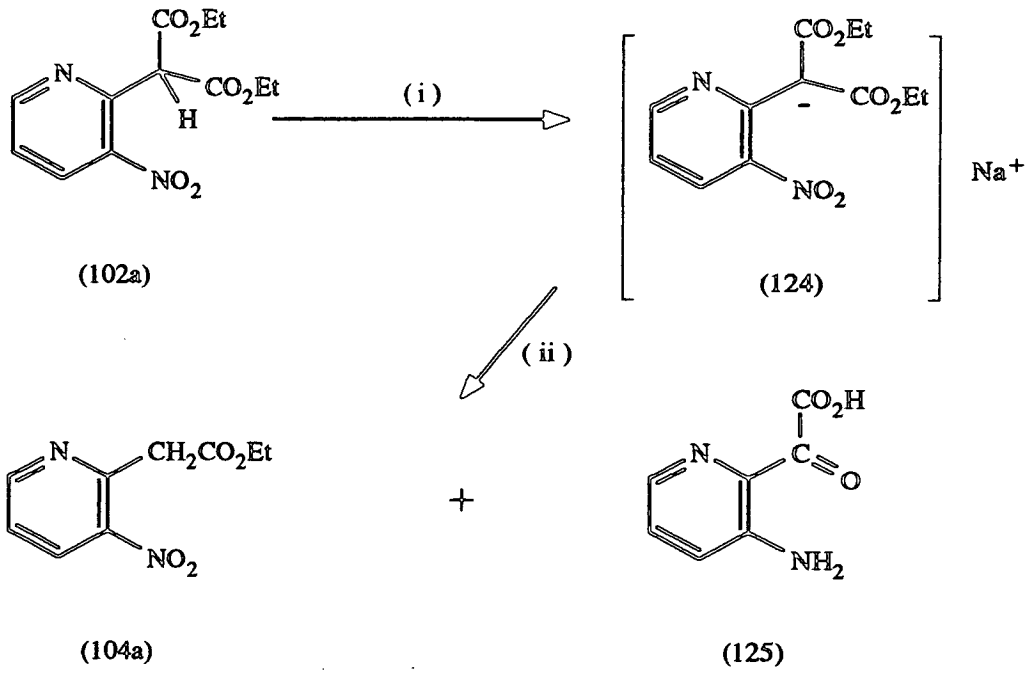
(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100°.
(ii) xylene, mol. sieves 5A, reflux.
(iii) pyridine, H_2O, reflux.

Scheme 33

would then explain the formation of the dibenzyl malonate derivative (102d). However this latter process does result in the removal of benzyl alcohol from the reaction mixture so by this note there should be an equivalent amount of the ethoxycarbonyl ketene (115) formed which cannot then equilibrate with the dialkyl malonate starting material (118). However any products arising from further transformations of the ketene (115) were not isolated from the crude reaction mixture and therefore the fate of the intermediate (115) is still uncertain at present. Having proposed a tenable mechanism (Scheme 31) for the transformation [(102) → (103)] the remainder of this section is concerned with experiments undertaken with a view to probing and hopefully elucidating the correct sequence of events during the fused 3,4-isoxazole synthesis currently under investigation.

It was initially believed that the leaving group capacity of the alcohol component of nitropyridylacetate derivatives is crucial for their efficient thermal conversion into isoxazolopyridines. It was therefore of interest to study the pyrolysis of a nitropyridyl malonic ester derivative of an alcohol which is a good leaving group. A suitable substrate for such a study was ethyl 4-nitrophenyl 2-(3-nitropyrid-2-yl)malonate. To this end ethyl 4-nitrophenyl malonate[51] was prepared as a precursor by the reaction of ethyl malonyl chloride with sodium 4-nitrophenolate and then the reaction of its anion with 2-chloro-3-nitropyridine (101) was attempted. However under the standard conditions employed for this type of condensation reaction all that was obtained was a high yield of 4-nitrophenol and therefore further attempts to perform this reaction were abandoned.

The next mechanistic aspect which was examined was the potential involvement of the nitro group as previously indicated (see Scheme 31) in the initial loss of a molecule of ethanol from the diester (102a) to give the ketene (115). Therefore (Scheme 33), the known[57] diethyl 2-(5-nitropyrid-2-yl)malonate (121) was straightforwardly prepared from 2-chloro-5-nitropyridine (120) and its pyrolysis in refluxing xylene solution with removal of ethanol by molecular sieves was examined.



(i) NaH, DME, room temp.
(ii) diglyme, reflux.

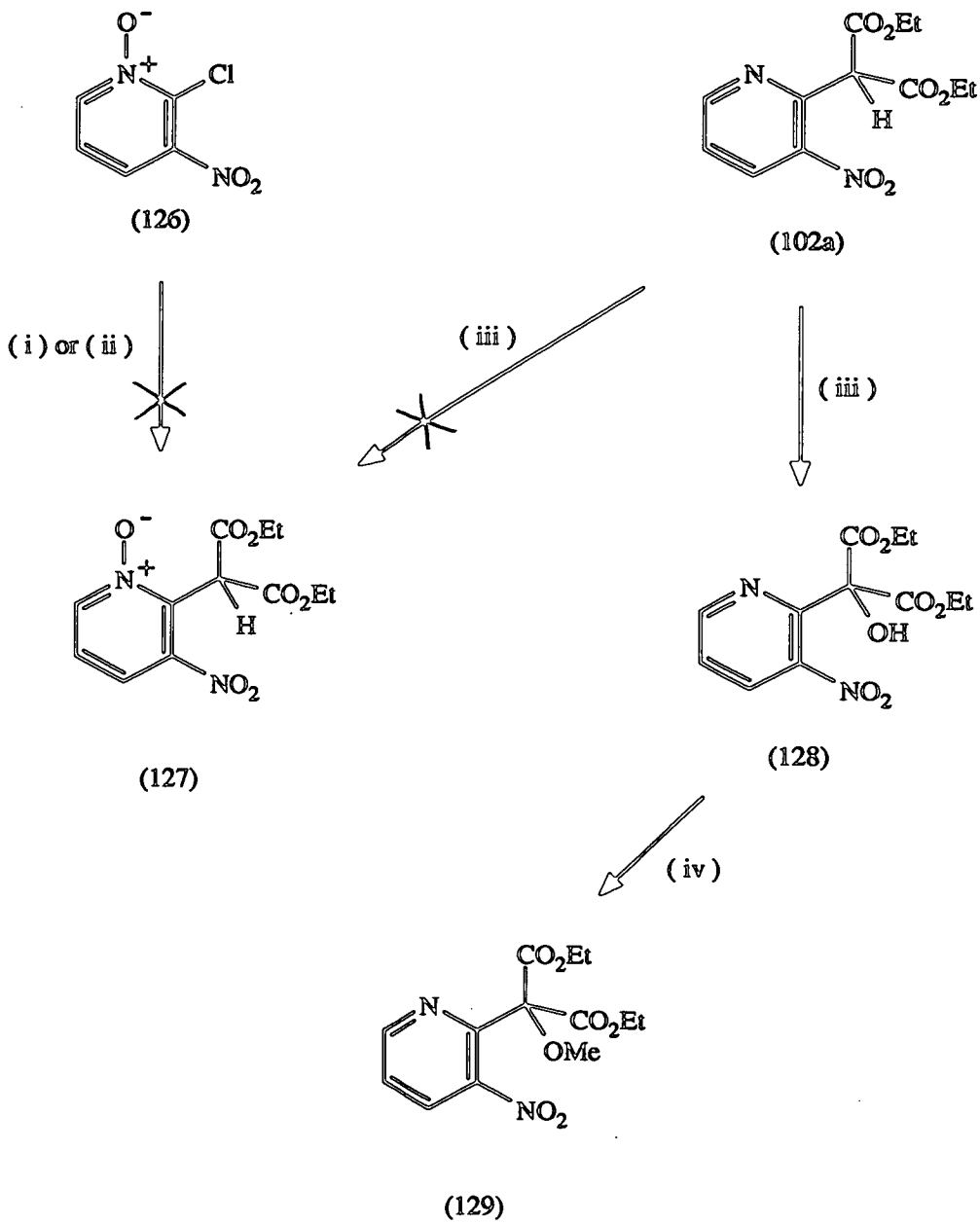
Scheme 34

These conditions resulted in almost complete consumption of the starting material after 48h to afford the nitropyridylacetate derivative (122) (16%) and a smaller amount of 2-methyl-5-nitropyridine (123) (6%), the remainder of the material comprising only an intractable mixture of products. As proof of structure, the nitropyridylacetate (122) was independently prepared in good yield (67%) by the pyrolysis of (121) in refluxing aqueous pyridine. The result for the pyrolysis of the diester (121) in xylene provides little insight into the reaction mechanism presently under study but does indicate that the thermal decomposition of the malonate side chain in (121), and therefore by analogy in the corresponding *ortho*-nitro isomer (102a), does not necessarily require participation of the nitro group. However, during the pyrolysis of the *para*-substituted nitropyridine (121) there is no convenient pathway for the decomposition to follow after the proposed ketene has been formed therefore explaining the low yields of identifiable products and the complex mixtures which were produced. However for the *ortho*-substituted nitropyridine (102a) further interaction of the nitro group with the adjacent ketene allows reaction to proceed in one favoured direction affording the isoxazolopyridine (103a) (see Scheme 31). The fact that the *para*-nitropyridylmalonate (121) requires 48h for almost complete consumption of the starting material whereas the *ortho*-nitro isomer (102a) requires only 24h does suggest that there is some involvement of the nitro group in the decomposition of the malonate side chain in the latter compound (102a).

It was then conjectured that increasing the mobility of the methine proton in the nitropyridylmalonate (102a) may improve the pyrolysis efficiency by making expulsion of ethanol to afford the proposed ketene intermediate (115) (Scheme 31) more facile. The main experimental evidence to support this claim comes from the fact that diethyl 2-(2-nitrophenyl)malonate (37b) and diethyl 2-(4-nitrophenyl)malonate underwent pyrolysis much more slowly (see later in Chapter 4) than their corresponding pyridine analogues. The extreme case was examined (Scheme 34) in which the methine proton of the diester(102a) was completely removed. Thus the sodium salt (124) of the diester

(102a) was prepared and its pyrolysis examined. However the sodium salt (124) was recovered unchanged from refluxing xylene solution after 24h, this failure to react perhaps being due to the fact that any extruded sodium ethoxide is not able to leave the reaction medium under these conditions. On the other hand, heating the salt (124) under reflux in the higher boiling solvent diglyme resulted in its complete consumption after only 2h to give, as the only identifiable products, a low yield of the nitropyridylacetate (104a) (30%) and a very low yield (7%) of a colourless semi-solid. The structure of this latter product was tentatively assigned as the amino acid derivative (125) on the basis of its i.r. spectrum and mass spectroscopic data. Unfortunately insufficient material was available to rigorously characterise the semi-solid (125) by its elemental analysis. This amino acid (125) may arise from the desired isoxazolopyridine product (103a) by the thermal or base-catalysed (by the extruded sodium ethoxide) opening of the isoxazole ring followed by some unspecified hydrogen abstraction step by the unstable nitrene intermediate produced. Ester hydrolysis to give the carboxylic acid may have been brought about by traces of water in the reaction mixture again perhaps catalysed by sodium ethoxide. The nitropyridylacetate (104a) is probably arising from a ketene intermediate produced by the pyrolysis of (124), as was described previously.

Notwithstanding the failure of the foregoing experiments to provide any valuable mechanistic information it was deemed appropriate to attempt to trap the postulated ketene intermediate (115) involved in the pyrolysis of the nitropyridylmalonate derivative (102a). Since *para*-benzoquinone is known to readily undergo [2+2] cycloaddition reactions with ketenes,[53] the pyrolysis of the nitropyridylmalonate (102a) was performed in the presence of this reagent [see Table 1; entry (xxii); facing page 22]. Unfortunately all that was obtained under these conditions was a good yield of the isoxazolopyridine (103a) and some unreacted *para*-benzoquinone, no products derived from the cycloaddition of *para*-benzoquinone to the ketene intermediate (115) being identified. As an alternative, an intramolecular

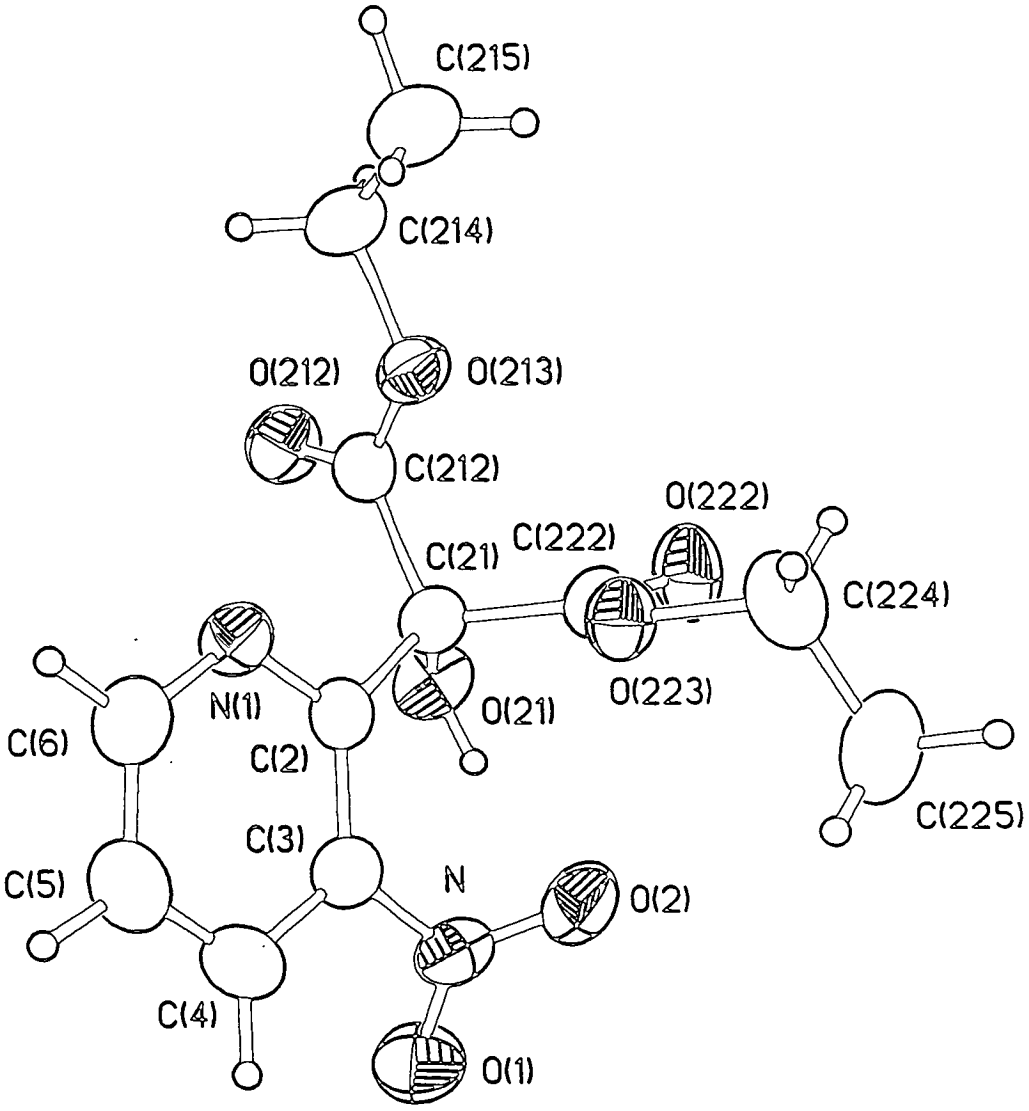


(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100°.
(ii) $CH_2(CO_2Et)_2$, NaH, DMF, room temp.
(iii) 90% H_2O_2 aqu., $(CF_3CO)_2O$, CH_2Cl_2, room temp.
(iv) MeI, NaH, room temp.

Scheme 35

ketene trap was sought and an appropriate substrate for this was considered to be (Scheme 35) the *N*-oxide derivative (127). It was speculated that during the pyrolysis of (127) the *N*-oxide functionality would be in suitable proximity to the ketene side-chain so as to interact in some way thus furnishing products which could be identified as arising from a ketene intermediate. Therefore, 2-chloro-3-nitropyridine-1-*N*-oxide (126) was prepared according to a literature procedure[54], but its reaction with the anion of diethyl malonate either at room temperature or at 100° disappointingly resulted in only the production of intractable, complex mixtures of products from which nothing could be identified. In an alternative approach to the *N*-oxide (127), the nitropyridylmalonate (102a) was oxidised under the conditions previously applied in the *N*-oxidation of 2-chloro-3-nitropyridine (101).[54] These conditions indeed resulted in the production of a colourless solid in high yield (73%) whose elemental analysis and mass spectrum both indicated that one atom of oxygen had been incorporated into the starting material (102a). However, the i.r. spectrum of this oxidised product shows a broad absorbtion at 3470 cm^{-1} and its ^1H n.m.r. spectrum exhibits a singlet resonance at $\delta_H = 4.83$ ppm which is completely removed on addition of deuterium oxide. All of this evidence suggests an alternative structure for the oxidised product, namely that of the 2-hydroxymalonate derivative (128). To confirm this structure an attempt was made to prepare its acetate derivative but (128) was recovered unchanged from refluxing acetic anhydride solution. However, the methyl ether (129) was readily prepared from the 2-hydroxymalonate (128) on treatment with sodium hydride and then with methyl iodide. The structure of the 2-hydroxymalonate (128) was finally, unequivocally established by X-ray diffraction analysis (see Figure 1 and Tables 4 and 5).

Further investigations concerning the scope, mechanism and synthetic utility of this interesting oxidation reaction [(102a) → (128)] were undertaken and will be discussed in Chapter 2, Section 2.4 of this thesis. However it was pertinent to the current mechanistic discussion to attempt the pyrolysis of the 2-hydroxymalonate


C(215)
C(214)
O(212)
O(213)
C(212)
O(222)
C(222)
C(21)
C(224)
N(1)
O(21)
O(223)
C(6)
C(2)
C(225)
C(3)
C(5)
N
O(2)
C(4)
O(1)

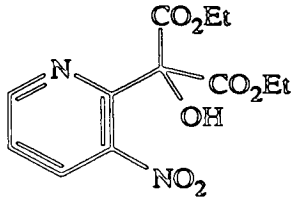

CO2Et
N
CO2Et
OH
NO2

Figure 1

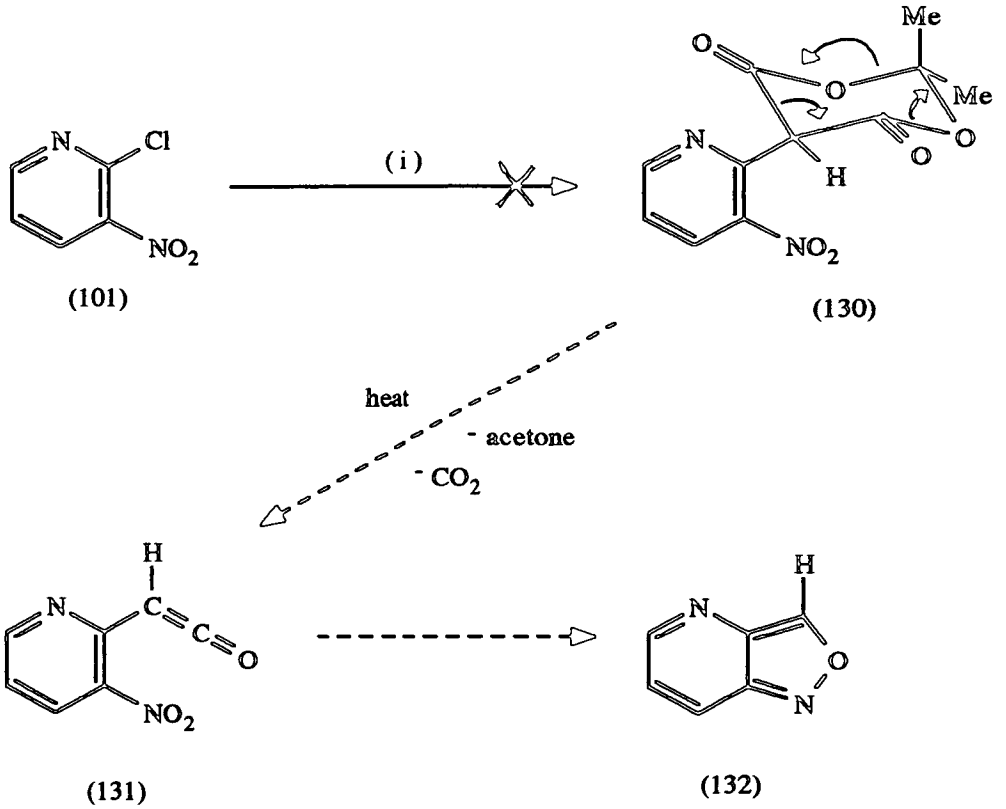
X-Ray Diffraction Data for Diethyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128)

Table 4 : Bond Lengths (Angstroms) with Standard Deviations

N(1) - C(2)	1.332 (3)	N(1) - C(6)	1.339 (4)
C(2) - C(3)	1.392 (4)	C(2) - C(21)	1.532 (4)
C(3) - C(4)	1.380 (4)	C(3) - N	1.465 (4)
C(4) - C(5)	1.367 (4)	C(5) - C(6)	1.374 (5)
C(21) - O(21)	1.395 (3)	C(21) - C(212)	1.541 (5)
C(21) - C(222)	1.546 (5)	C(212) - O(212)	1.200 (5)
C(212) - O(213)	1.316 (3)	O(213) - C(214)	1.466 (4)
C(214) - C(215)	1.480 (5)	C(222) - O(222)	1.197 (3)
C(222) - C(223)	1.315 (4)	O(223) - O(224)	1.459 (5)
C(224) - C(225)	1.474 (6)	N - O(1)	1.211 (3)
N - O(2)	1.217 (4)		

Table 5 : Bond Angles (Degrees) with Standard Deviations

C(2) - N(1) - C(6)	118.9 (2)	N(1) - C(2) - C(3)	119.9 (2)
N(1) - C(2) - C(21)	116.4 (2)	C(3) - C(2) - C(21)	123.5 (2)
C(2) - C(3) - C(4)	120.9 (3)	C(2) - C(3) - N	121.7 (2)
C(4) - C(3) - N	117.4 (3)	C(3) - C(4) - C(5)	118.2 (3)
C(4) - C(5) - C(6)	118.5 (3)	N(1) - C(6) - C(5)	123.4 (3)
C(2) - C(21) - O(21)	109.8 (2)	C(2) - C(21) - C(212)	107.6 (2)
O(21) - C(21) - C(222)	108.8 (3)	C(2) - C(21) - C(22)	113.6 (3)
O(21) - C(21) - C(212)	108.9 (2)	C(212) - C(21) - C(222)	108.0 (2)
C(21) - C(212) - O(212)	120.9 (2)	C(21) - C(212) - O(213)	112.7 (3)
O(212) - C(212) - O(213)	126.5 (3)	C(212) - O(213) - C(214)	116.6 (3)
O(213) - C(214) - C(215)	105.7 (3)	C(21) - C(222) - O(222)	121.7 (3)
C(21) - C(222) - O(223)	112.7 (2)	O(222) - C(222) - O(223)	125.5 (3)
C(222) - O(223) - C(224)	116.1 (2)	O(223) - C(224) - C(225)	111.5 (3)
C(3) - N - O(1)	118.0 (3)	C(3) - N - O(2)	118.2 (2)
O(1) - N - O(2)	123.7 (3)		

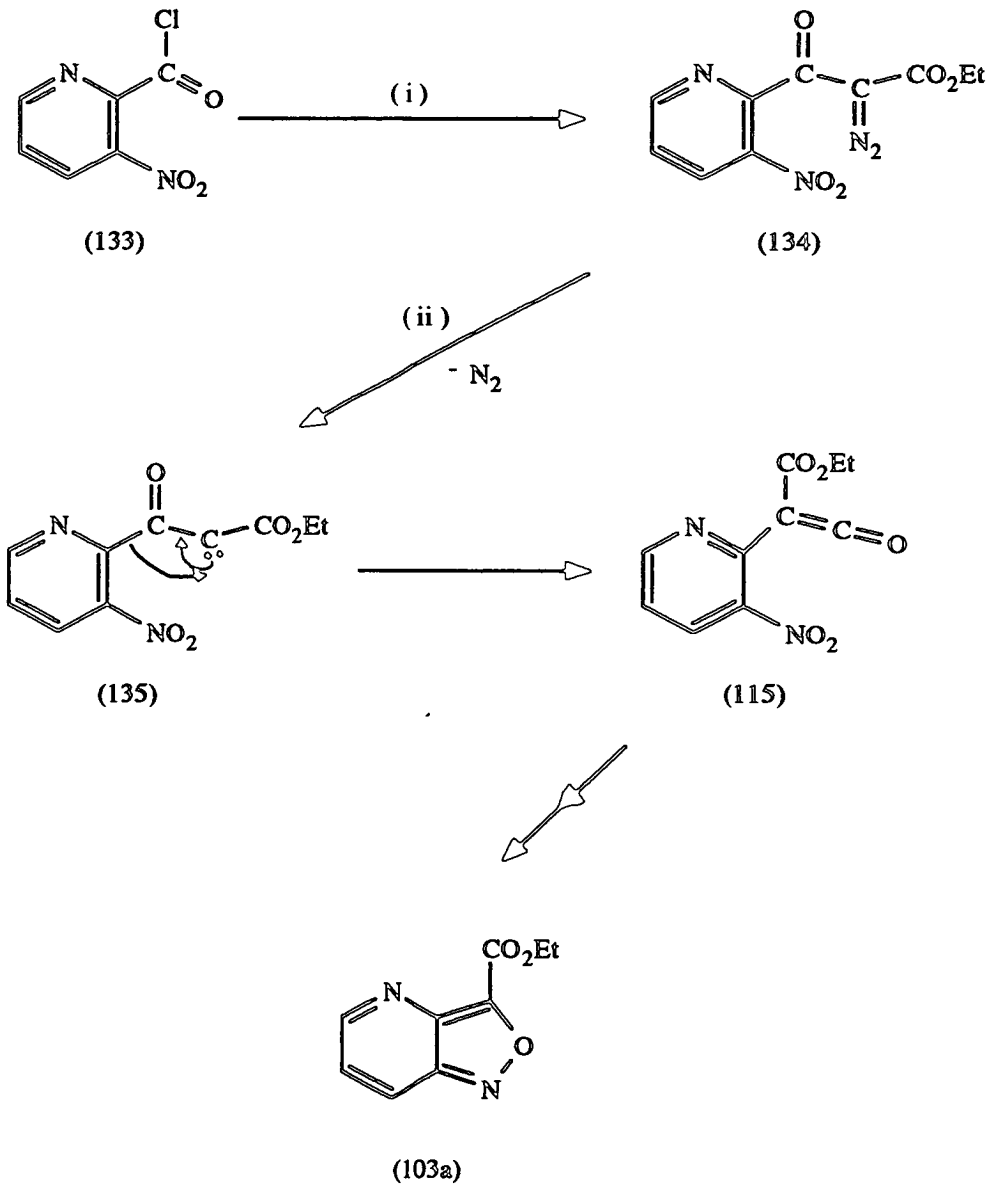


(i) Meldrum's acid, NaH, DMF, 100°.
(ii) Meldrum's acid, NaH, DMF, room temp.

Scheme 36

derivative (128) but, in line with the proposed mechanism wherein a mobile methine proton is required on the malonate side chain to allow loss of a molecule of ethanol, this compound was recovered unchanged in high yield from refluxing xylene solution after 24h with provision having been made for the removal of ethanol by molecular sieves.

Since the attempted trapping of a possible ketene intermediate, either intermolecularly or intramolecularly, proved to be fruitless it was instead attempted to synthesise the ketene intermediate (115) or an analogous derivative thereof by an independent route. The first such approach (Scheme 36) involved the preparation of the Meldrum's Acid derivative (130) and the study of its thermal behaviour. Since Meldrum's Acid derivatives are well known to eliminate carbon dioxide and acetone on heating to afford ketenes[55] it was hoped that if the pyrolysis of the nitropyridine (130) afforded the isoxazolo[4,3-b]pyridine derivative (132) then this would provide strong evidence for the ketene intermediate (131) and therefore by analogy the possible intermediacy of the ketene (115) during the pyrolysis of the nitropyridylmalonate (102a) to afford the isoxazolopyridine (103a) (see Scheme 31; facing page 33). However, it was unfortunate to find that all attempts to condense the anion of Meldrum's Acid with 2-chloro-3-nitropyridine (101) failed, resulting in either recovery of the unreacted starting materials or in decomposition leading to intractable mixtures. Despite this disappointing failure, a second approach to the synthesis of a 2-nitropyridylketene derivative was investigated (Scheme 37), this procedure relying on the well known Wolff rearrangement of α-diazoketones to afford ketenes.[56] In this context the diazo derivative (134) was required and this was readily prepared by the reaction of 3-nitropyridine-2-carboxylic acid chloride (133) with ethyl diazoacetate under literature conditions previously reported for the successful condensation of ethyl diazoacetate with acid chlorides.[57] The preparation of the requisite acid chloride (133) by an interesting new route starting from 2-chloro-3-nitropyridine (101) will be discussed in detail in Chapter 2, Section 2.4 of this thesis.



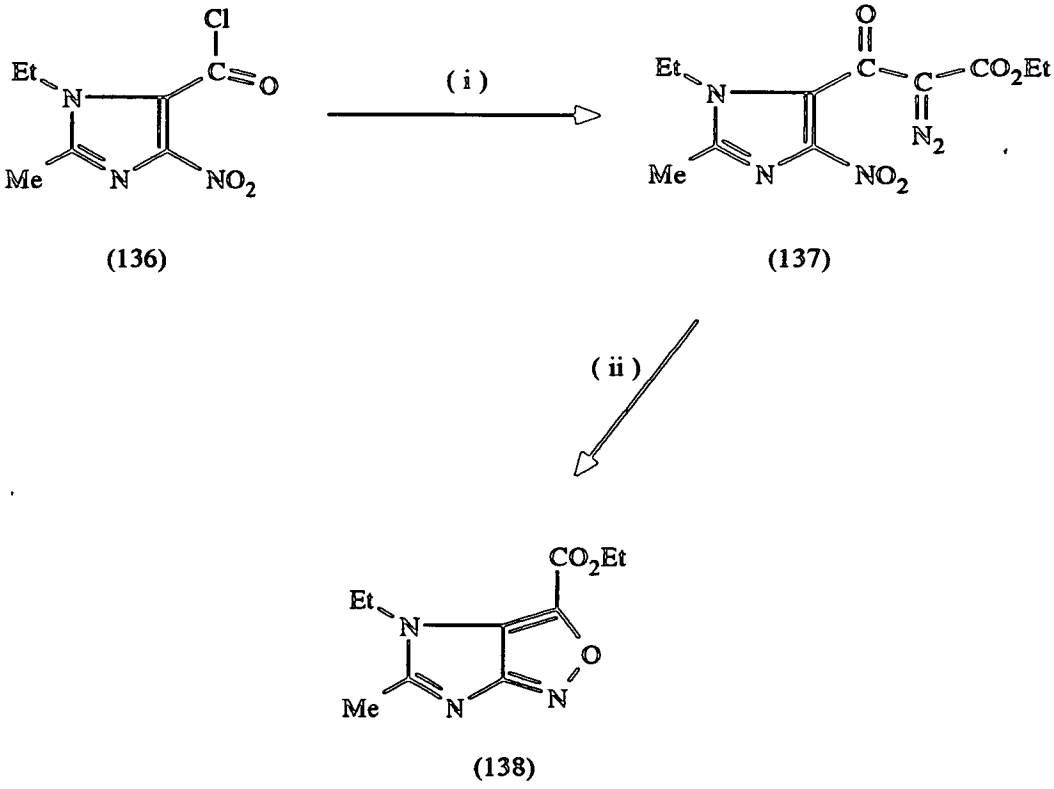
(i) ethyl diazoacetate, 50°.
(ii) toluene, reflux.

Scheme 37

It was very pleasing to discover that on heating the diazo compound (134) under reflux in toluene the isoxazolopyridine (103a) was indeed produced, albeit in only 23% yield, and was identical in all respects to a sample obtained via the pyrolysis of the nitropyridylmalonate derivative (102a). This transformation is readily explained by thermal extrusion of nitrogen from (134) leading firstly to the carbene (135) which can then undergo Wolff rearrangement with shift of the pyridine ring to afford the ketene intermediate (115). Further transformation of the ketene intermediate (115) into the isoxazolopyridine (103a) has already been postulated (see Scheme 31; facing page 33).

The successful thermolysis of the diazo compound (134) to afford the isoxazolopyridine (103a) does not unequivocally prove the intermediacy of the ketene (115) during the pyrolysis of the nitropyridylmalonate (102a) to afford the isoxazolopyridine (103a). However it does provide very strong evidence that if the ketene (115) is indeed produced by the pyrolysis of the nitropyridyl malonate (102a), then it can further transform into the isoxazolopyridine (103a). The low yield of the isoxazolopyridine (103a) from the pyrolysis of the diazo compound (134) may be due to other reactions of the carbene intermediate (135) by any of a number of different routes leading to the multicomponent mixtures which were produced along with (103a).

Finally, as a further example to show that the pyrolysis of appropriate diazo compounds can afford fused 3,4-isoxazoles (Scheme 38) the imidazole derivative (137) was prepared from the readily available acid chloride (136)[58] and its pyrolysis investigated. It was gratifying to find that heating the diazo compound (137) under reflux in toluene did indeed afford the known[58] imidazo[3,4-d]isoxazole derivative (138) in 60% yield. Although this fused 3,4-isoxazole synthesis via the pyrolysis of diazoketones has provided valuable insight into the mechanism for the pyrolysis of the 2-nitro heteroaromatic malonate derivatives presently under investigation, further



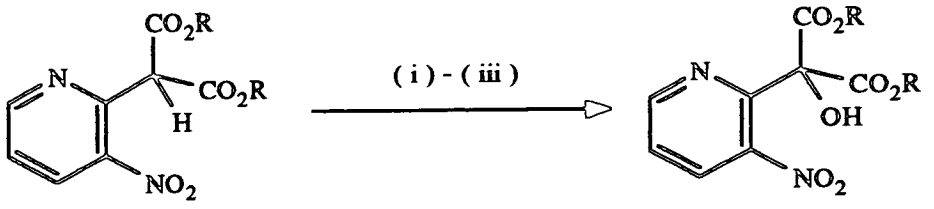
(136) (137) (138)

(i) ethyl diazoacetate, 50°.
(ii) toluene, reflux.

Scheme 38

investigations on the optimisation of this alternative pyrolysis reaction and its potential exploitation in heterocyclic synthesis were not undertaken during the present studies.

To sum up the mechanistic information that was gathered on the pyrolysis of the nitropyridylmalonate derivative (102a) to afford the isoxazolopyridine (103a), strong evidence has been accumulated for the intermediacy of a 2-nitropyridylketene intermediate. Also it would appear that decomposition of the malonate derivatives under study is facilitated by increasing the mobility of the methine proton in the malonate side chain and by the presence of an *ortho*-nitro substituent.

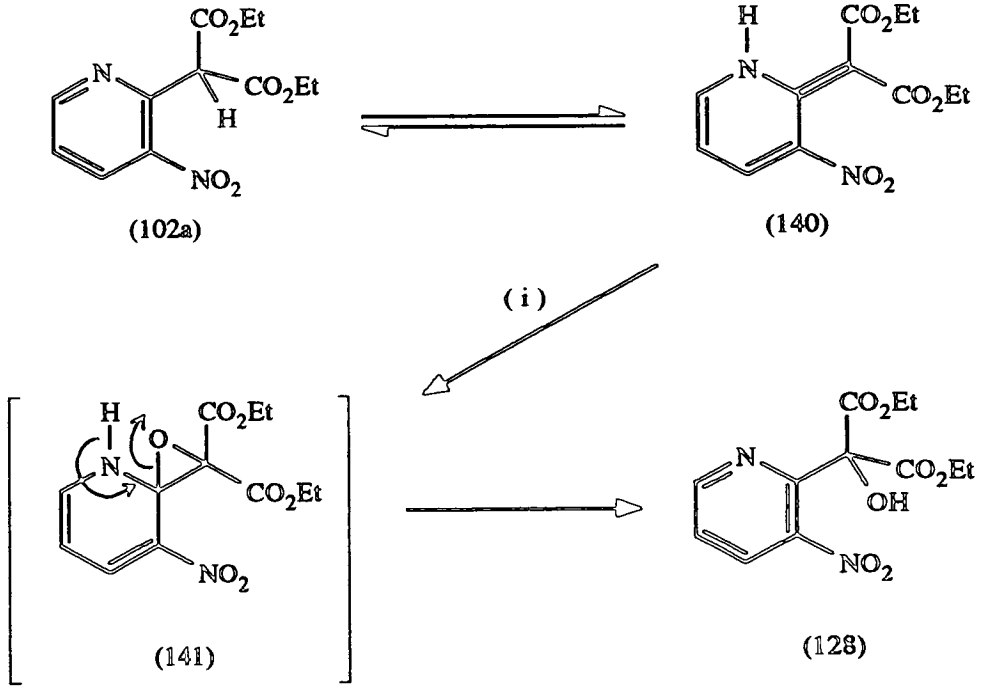


(102) R
a ; Et
b ; Me
c ; t-Bu

R
(128) ; Et
(139a) ; Me
(139b) ; t-Bu

(i) 30% H_2O_2 aqu., AcOH, 50°.
(ii) 30% H_2O_2 aqu., 1M NaOH aqu., room temp.
(iii) MnO_2, MeCN, room temp.

Scheme 39



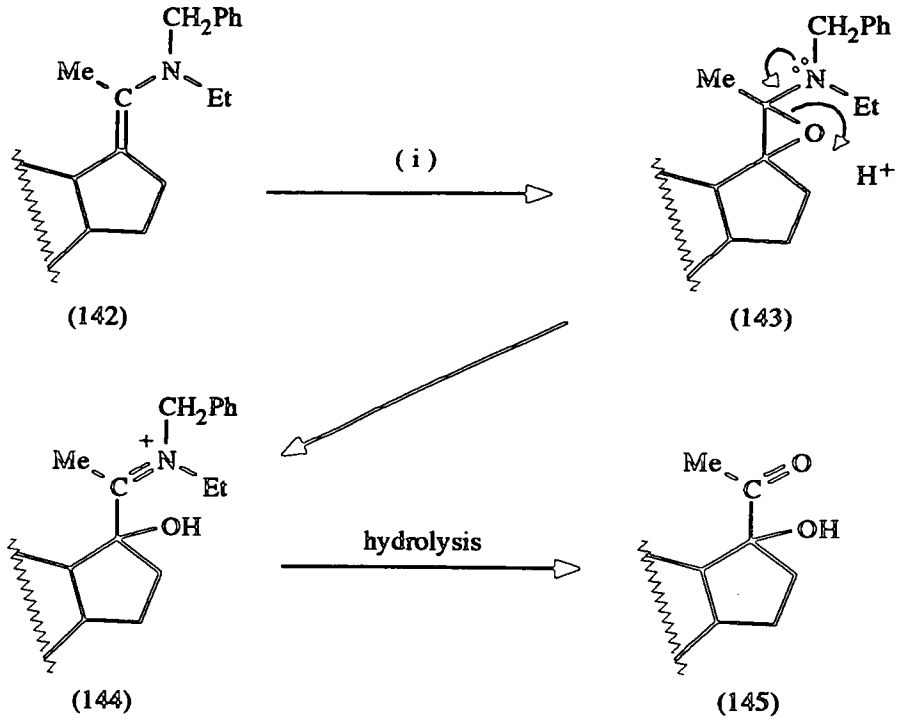
(i) 30% H_2O_2 aqu., AcOH, 50°.

Scheme 40

2.4 : Investigations on the Side-Chain Oxidation of Pyridine Derivatives

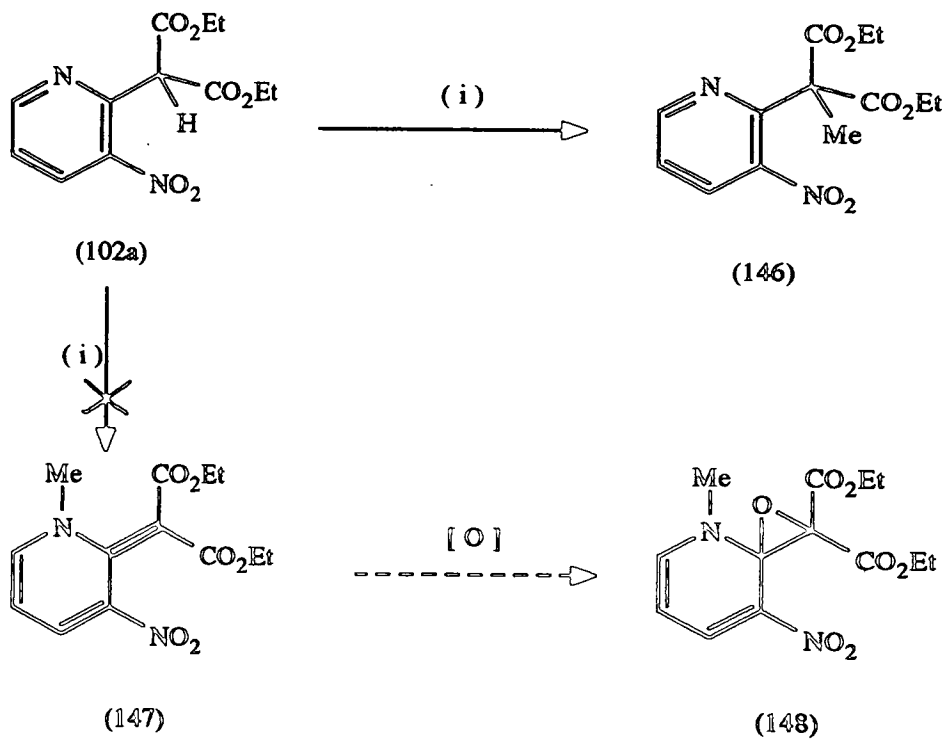
The following section is concerned with an investigation into the scope, mechanism and synthetic utility of the interesting oxidation reaction (Scheme 39) which was discovered by chance during the studies presently under discussion. As briefly discussed in the previous section the nitropyridylmalonate derivative (102a) was converted in good yield into the 2-hydroxymalonate derivative (128) on treatment with trifluoroperacetic acid. An initial investigation of this type of transformation using alternative oxidising agents revealed that the process [(102a) → (128)] could also be brought about by peracetic acid in excellent yield (87%), by alkaline hydrogen peroxide in 64% yield and also by activated manganese dioxide in 58% yield. Not surprisingly, the analogous dimethyl malonate derivative (102b) was also oxidised in a similar manner by peracetic acid to afford the dimethyl 2-hydroxymalonate (139a) in good yield (70%). However treatment of the di-*tert*-butyl malonate derivative (102c) with peracetic acid gave only a low yield (15%) of the corresponding oxidised product (139c), this result perhaps being due to steric hindrance by the two bulky *tert*-butyl groups to approach by the oxidising agent.

The fact that such a diverse array of oxidising agents are able to effect the transformation [(102a) → (128)] is remarkable and it is probable that different mechanisms are in operation for each reagent. A plausible mechanistic pathway for the peracid oxidation of the diester (102a) is outlined in Scheme 40 and involves the initial epoxidation of the enamine tautomer (140) of the diester (102a) followed by acid-catlaysed rearrangement of the epoxidation product (141) to finally furnish the 2-hydroxymalonate derivative (128). The imine-enamine tautomerism [(102a)⇌(140)] of such substituted pyridine derivatives which is a key step in this mechanism is well known[59] and although the ^{1}H n.m.r spectrum of the diester (102a) does not show any evidence for the presence of the enamine tautomer (140) in either deuteriochloroform or hexadeuterio dimethylsulphoxide solution this does not preclude the formation of



(i) perbenzoic acid.

Scheme 41



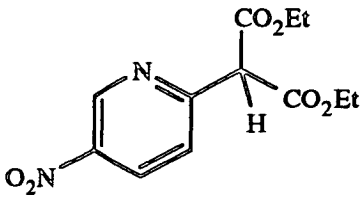
(i) MeI, NaH, DMF, room temp.

Scheme 42

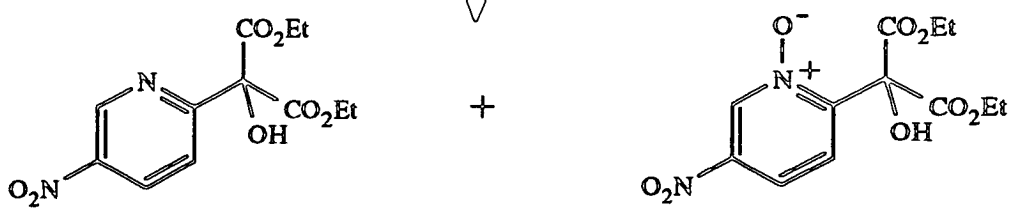
the enamine (140) in acetic acid solution under the oxidation conditions. Enamines are known to react with peracids in the manner outlined in Scheme 40 as illustrated by an example from the field of steroid chemistry[60] (Scheme 41) wherein the enamine (142) was treated with perbenzoic acid to afford the α-hydroxyketone (145). This transformation is proposed to occur via initial epoxidation of the enamine (142) to give epoxide (143) which then undergoes rearrangement to afford the quaternary iminium salt (144) whose subsequent hydrolysis finally yields the α-hydroxyketone (145).

To substantiate the mechanism proposed in Scheme 40, an attempt was made (Scheme 42) to trap the enamine tautomer (140) by its methylation to give the conjugated diester derivative (147) and then to subject (147) to peracid oxidation in the hope of isolating the epoxide derivative (148). Methylation of the diester (102a) indeed gave a monomethyl derivative in excellent yield (81%) but the i.r and ^{1}H and ^{13}C n.m.r spectra and were all in accord with the structure (146) for the product wherein C-methylation has occurred with no detectable amounts of the desired methylated derivative (147) present.

The oxidation of the nitropyridylmalonate (102a) by manganese dioxide cannot be rationalised by an epoxidation mechanism and more than likely is occuring via initial hydrogen abstraction at the benzylic position by the manganese dioxide to give a highly stabilised radical intermediate. The mode of insertion of the oxygen atom is uncertain but it has been proposed for similar examples in the literature that during the manganese dioxide mediated oxidation of, for example triphenylmethane to afford triphenylmethanol,[61] the manganese dioxide itself provides the oxygen atom that ultimately appears in the product. Alternatively manganese dioxide catalysed autoxidation with incorporation of molecular oxygen would give initially a hydroperoxy species also via a radical mechanism which could then decompose to afford the hydroxy product (128). This latter mechanism is favoured due to the observation that the nitropyridylmalonate (102a) is recovered unchanged when treated



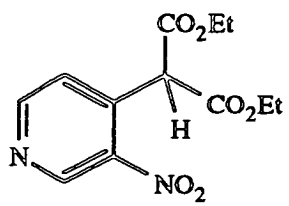
(121)



(149) (150)

(i) 30% H_2O_2 aqu., AcOH, 50°.

Scheme 43



(111)

(151) (152)

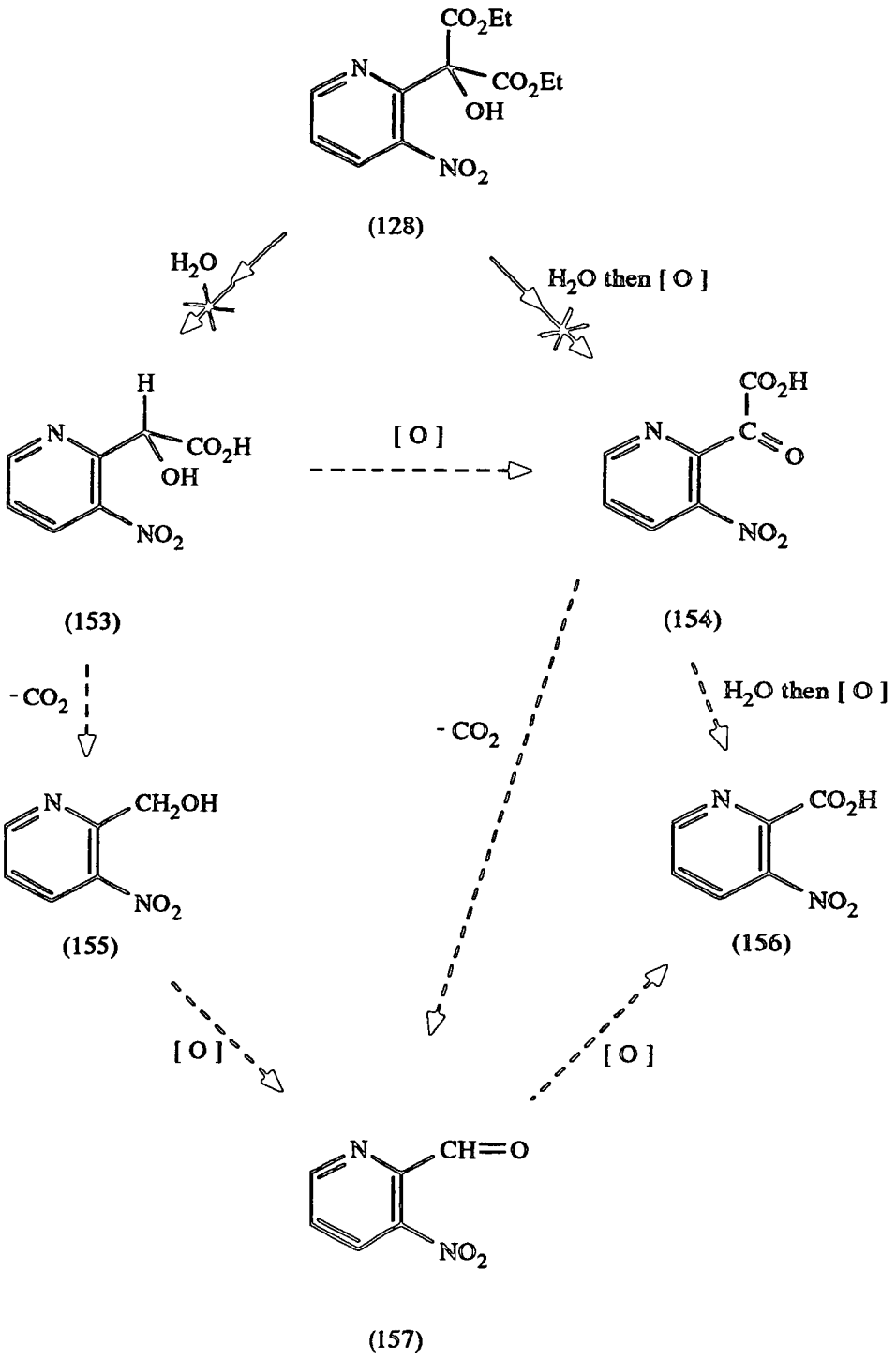
(i) 30% H_2O_2 aqu., AcOH, 50°.
(ii) MnO_2, MeCN, room temp.

Scheme 44

with activated manganese dioxide under a nitrogen atmosphere where no molecular oxygen is present.

The oxidation of the nitropyridylmalonate (102a) by alkaline hydrogen peroxide is yet more puzzling and may involve nucleophilic addition of hydroperoxy anion to a tautomeric species such as the enamine tautomer (140) (see Scheme 40) or possibly occurs through oxidation of some carbanionic or radical species, the exact details of which remain unclear at present. Similar base-catalysed oxidation reactions are known, examples being the facile autoxidation of the three isomeric methylpyridines[62] catalysed by potassium *tert*-butoxide to furnish the respective pyridine carboxylic acids or the production of triphenylmethanol and triphenylmethanol hydroperoxide on treatment of triphenylmethane with molecular oxygen catalysed by a variety of bases.[63] However a mechanism for the alkaline hydrogen peroxide mediated oxidation of the diester (102a) to afford the 2-hydroxymalonate derivative (128) is not immediately obvious at present.

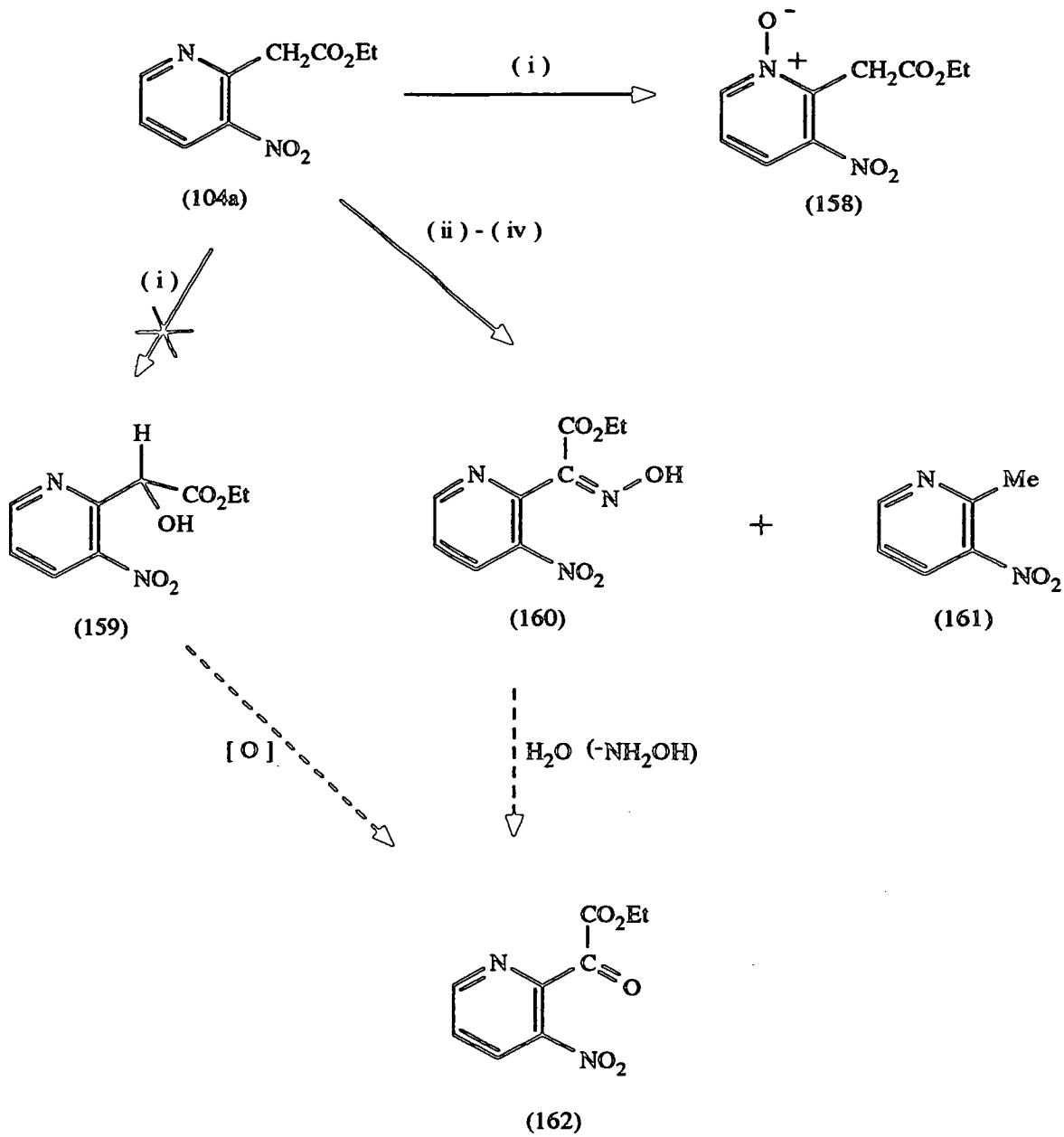
In an investigation of the type of substrates capable of undergoing C-hydroxylation (Scheme 43), diethyl 2-(5-nitropyrid-2-yl)malonate (121) was treated with peracetic acid and yielded two products. The major product, isolated in 60% yield, was found to be the expected 2-hydroxymalonate derivative (149) while the minor product (8%) was found to be derived by the incorporation of two atoms of oxygen this product being assigned the pyridyl-2-hydroxymalonate *N*-oxide structure (150). The production of some of the *N*-oxide (150) in this case may be due to the fact that the pyridine nitrogen atom in (121) is slightly less crowded than that of the isomeric compound (102a) since removing the nitro group from the position adjacent to the malonate side chain to the *para* position as in (121) allows the side chain to be further away from the pyridine nitrogen atom. This decrease in steric hindrance would make access of the oxidising agent to the pyridine nitrogen atom somewhat more facile.


CO2Et
N
CO2Et
OH
NO2
(128)
H2O
H2O then [O]
H
N
CO2H
OH
NO2
[O]
CO2H
C
O
N
NO2
(153)
(154)
- CO2
- CO2
H2O then [O]
N
CH2OH
NO2
N
CO2H
NO2
(155)
(156)
[O]
[O]
N
CH=O
NO2
(157)

Scheme 45

It was of interest (Scheme 44) to study the oxidation of diethyl 2-(3-nitropyrid-4-yl)malonate (111) to acertain whether the pyridine nitrogen atom needs to be adjacent to the malonate side chain for successful oxidation of the latter. In practice, peracetic acid oxidation of (111) gave only a low yield (19%) of a colourless, crystalline solid whose elemental analysis and mass spectrum indicated that two atoms of oxygen had been incorporated. This product is therefore assigned the pyridyl-2-hydroxymalonate-*N*-oxide structure (151) and this result further demonstrates that decreasing the steric hindrance at the pyridine nitrogen atom facilitates its *N*-oxidation. The nitropyridylmalonate (111) was also found to be oxidised by activated manganese dioxide, albeit in only 27% yield, to give a mono-oxygenated product assigned the 2-hydroxymalonate structure (152). The reason for the low yields obtained in the oxidation reactions of the diester (111) remains unclear at the present but may indicate that the adjacency of a ring nitrogen atom facilitates oxidation of the malonate side chain.

It was hoped that the 2-hydroxymalonate derivatives synthesised in the course of the present studies could be turned to some use by their conversion into usefully functionalised 3-nitropyridine derivatives (Scheme 45). The synthesis of substituted nitropyridines has been recently reviewed[64] and they are known to be useful synthetic intermediates in the manufacture of medicinal agents[65,66] and dyestuffs[67] and are also precursors in the synthesis of a myriad of heterocyclic compounds such as napthyridines,[68] pyrrolopyridines[69] and pyridodiazines.[70] However nitropyridine derivatives containing oxidised functional groups such as those depicted in Scheme 45 are notoriously difficult to synthesise[71,72,73] so it was hoped that the hydrolysis or oxidation of the 2-hydroxymalonate derivative (128) would in some way allow access to these derivatives [(153 to (157)]. Unfortunately all attempts to hydrolyse (128) under acidic or basic conditions resulted in complete decomposition of the starting material into intractable materials as did attempts to oxidise (128) with either chromic acid or alkaline hydrogen peroxide.



(i) 30% H_2O_2 aqu., AcOH, 50°.

(ii) i-$C_5H_{11}ONO$, NaOEt, EtOH, room temp.

(iii) i-$C_5H_{11}ONO$, NaH, DME, 50°.

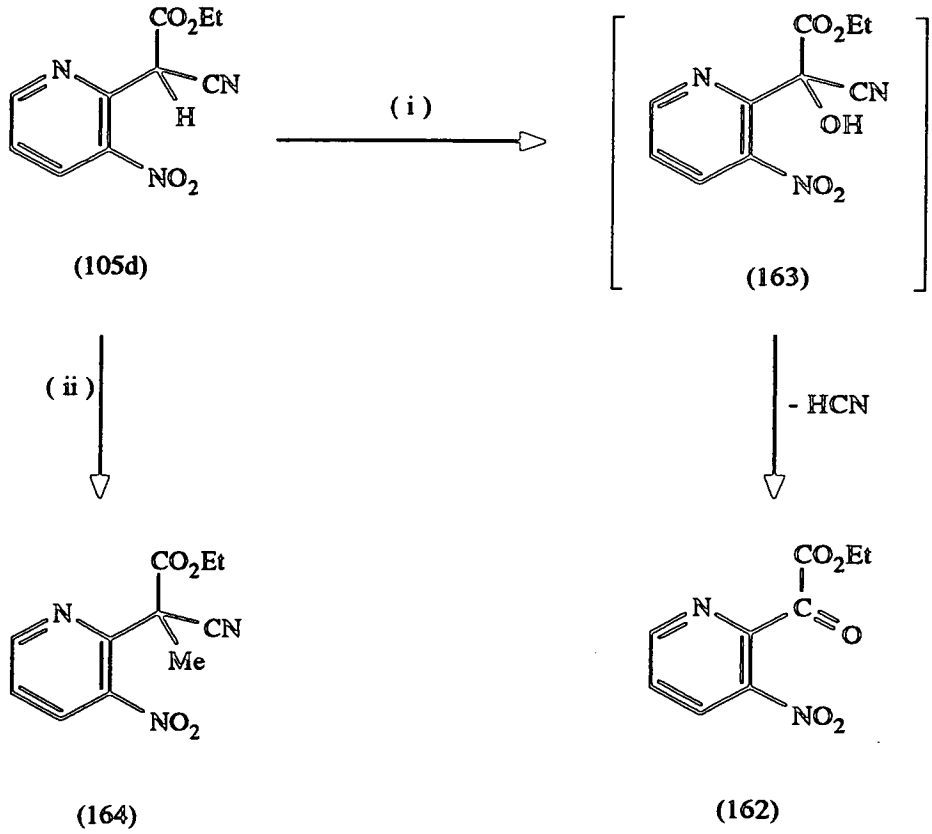
(iv)EtONO, NaOEt, EtOH, room temp.

Scheme 46

A further attempt (Scheme 46) to obtain an oxidised nitropyridine derivative, the 2-hydroxyacetate derivative (159), by the oxidation of ethyl 2-(3-nitropyrid-2-yl)acetate (104a) resulted only in the isolation in low yield (15%) of a compound which had incorporated one atom of oxygen but was subsequently identified as the pyridine-*N*-oxide derivative (158) rather than the hydroxy compound (159).

An alternative method for the preparation of nitropyridines with oxidised side chains from the nitropyridylacetate derivative (104a) was next investigated but also proved to be unsuccessful. It was initially hoped that if the oxime (160) could be prepared from the nitropyridylacetate (104a) then hydrolysis of the oxime (160) would afford the ketoester derivative (162). The sodium ethoxide catalysed reaction of the monoester (104a) with isoamyl nitrite did indeed form the desired oxime derivative (160) but in only 19% yield. The major product of this reaction was in fact 2-methyl-3-nitropyridine (161) the structure of which was proven by its comparison with an authentic sample prepared by a literature method.[43] Using sodium hydride as the base in this type of transformation unfortunately resulted only in a high yield of the unwanted methyl compound (161) as the sole product. Conversely changing the nitrosating agent to ethyl nitrite gave no improvement (18%) in the yield of the desired oxime (160) over that obtained using isoamyl nitrite. The 2-methyl-3-nitropyridine by-product (161) presumably arises from the acetate derivative (104a) by either hydrolysis followed by decarboxylation or by base-catalysed retro-Claisen reaction of the monoester (104a) with loss of the ethoxycarbonyl functionality. This speculative approach to the ketoester derivative (162) involving the formation and subsequent hydrolysis of the oxime (160) was abandoned at this point in the light of the successful synthesis of the ketoester (162) which will now be discussed.

Another method investigated for the synthesis of nitropyridine derivatives with oxidised side chains (Scheme 47) involved the treatment of the cyanoacetate derivative (105d) with peracetic acid. This reaction afforded a yellow solid in 49% yield whose elemental analysis and spectroscopic data were all in agreement with its formulation as



(i) 30% H_2O_2 aqu., AcOH, 50°.
(ii) MeI, NaH, DMF, room temp.

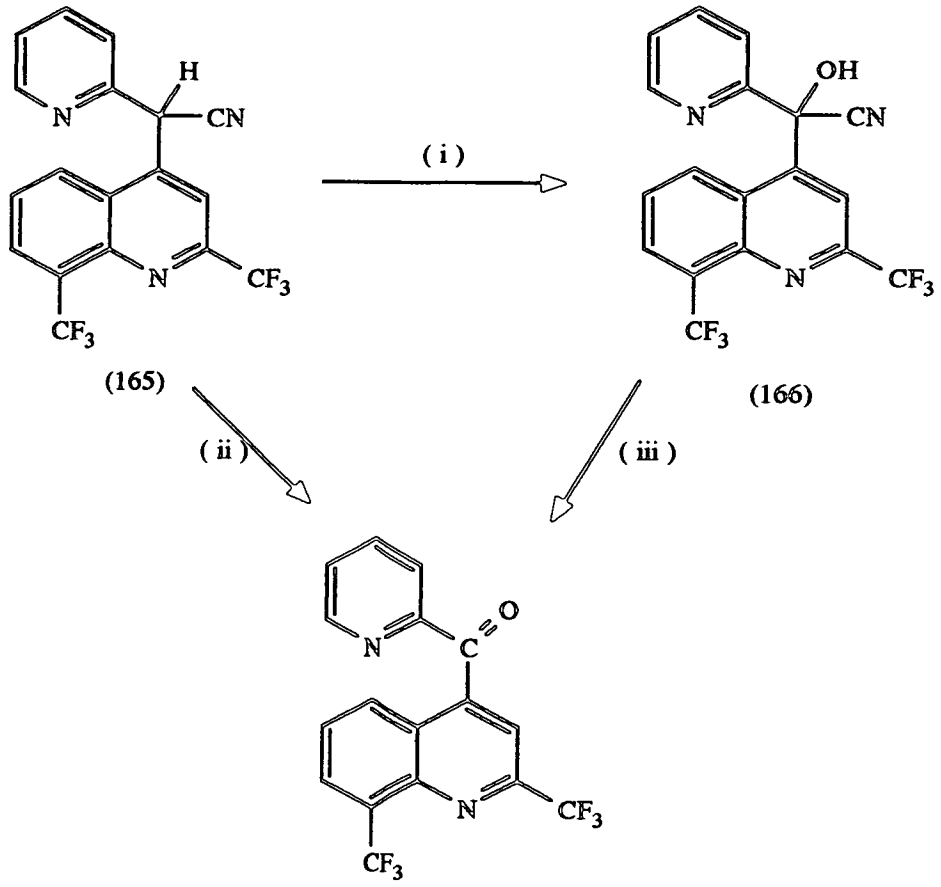
Scheme 47

the desired ketoester derivative (162). This oxidation reaction presumably involves initial epoxidation of the enamine tautomer of (105d) followed by rearrangement to give the cyanohydrin intermediate (163) which then readily eliminates hydrogen cyanide to finally afford the ketoester (162). All attempts to improve the yield of the ketoester (162) by using alternative reagents for the oxidation of the cyanoacetate (105d) were unsuccessful. Alkaline hydrogen peroxide oxidation of the cyanoacetate (105d) lead to the production of only intractable mixtures of products while attempted manganese dioxide oxidation of (105d) gave only a high yield of unreacted starting material.

Again it was of interest to attempt to trap the enamine tautomer of (105d) as its *N*-methyl derivative particularly since the cyanoacetate (105d) shows a greater propensity for this type of tautomerism than the malonate derivative (102a) for which a similar trapping experiment was attempted (see before). A high yield of a monomethyl derivative was indeed produced from the cyanoacetate (105d) whose i.r. and ^{1}H and ^{13}C n.m.r. spectra unfortunately indicate that it is the undesired C-methyl derivative (164).

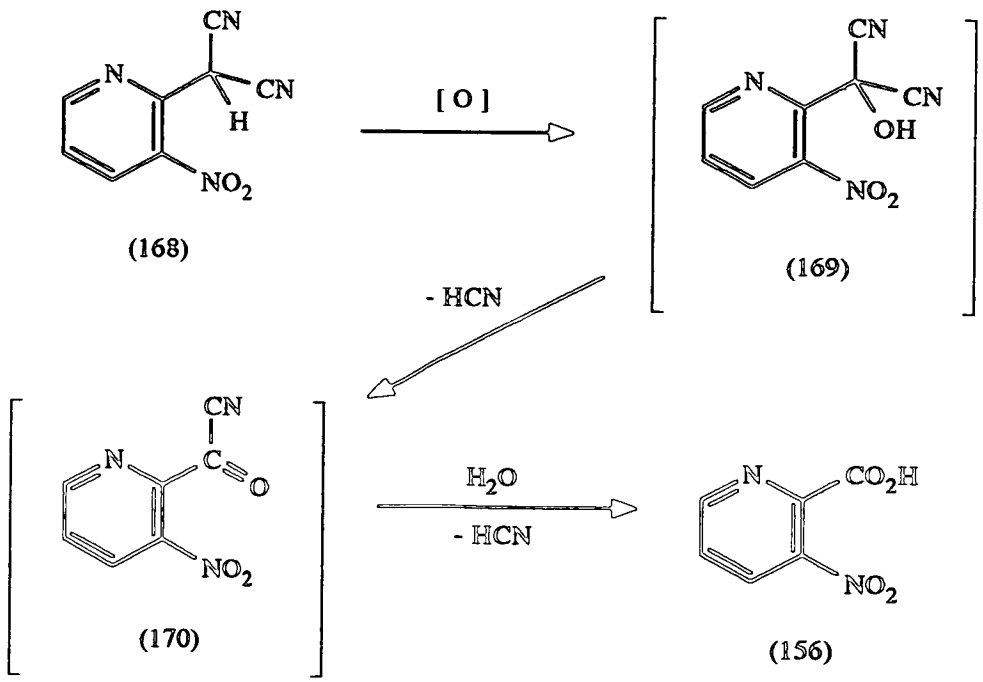
All attempts to degrade the ketoester derivative (162) to other side-chain oxidised derivatives by hydrolysis with either acid or base proved to be fruitless, these reactions giving only unreacted starting materials or resulting in the complete decomposition of the ketoester (162) into intractable materials.

It should be noted at this point that while the present studies were in progress a paper was published by the Hoffman-la-Roche company[74] (Scheme 48) which reported that in an attempt to obtain the *N*-oxide of the pyridylacetonitrile derivative (165) by oxidation with *meta*-chloroperbenzoic acid (mCPBA) the product isolated was the cyanohydrin (166) which was then further hydrolysed to the 2-acylpyridine derivative (167). The author also reports that peracetic acid converts the pyridylacetonitrile (165) directly into the 2-acylpyridine (167). A mechanism for this transformation was also postulated analogous to that independently proposed (see



(i) *meta*-chloroperbenzoic acid, Et_2O, room temp.
(ii) 30% H_2O_2 aqu., AcOH, 50°.
(iii) NaOH aqu., room temp.

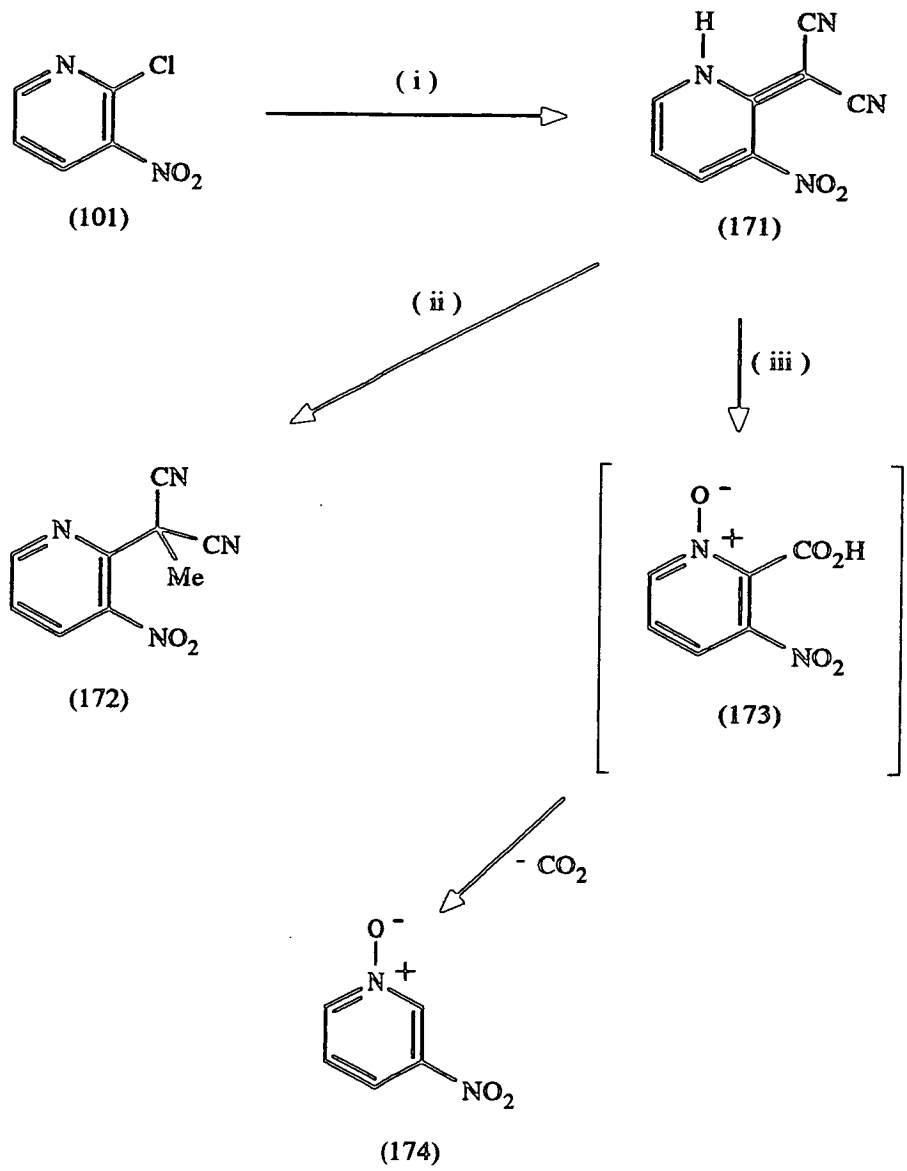
Scheme 48



Scheme 49

Schemes 40 and 47) for the oxidation of nitropyridine derivatives investigated in the present studies.

Of most interest (Scheme 49) is the potential application of this type of oxidation procedure for the synthesis of 3-nitropicolinic acid (156). The only method currently available for the synthesis of this potentially synthetically useful carboxylic acid is via permanganate oxidation of 2-methyl-3-nitropyridine.[71] However the harsh conditions required for this reaction result in low and often variable yields of the desired acid.[71,72] It would be of great advantage if a high yielding, reproducible method for the preparation of 3-nitropicolinic acid (156) was available since its value as an intermediate in heterocyclic synthesis could then be more readily explored and also because derivatives of (156) have been shown to possess biological activity.[75] Therefore it was anticipated that oxidation of the pyridylmalononitrile derivative (168) should give the dicyanohydrin (169) which would then eliminate hydrogen cyanide to give the highly reactive acyl cyanide intermediate (170). In situ hydrolysis of the latter would then afford the desired 3-nitropicolinic acid (156). In practice (Scheme 50), the anion of malononitrile reacted readily with 2-chloro-3-nitropyridine (101) to afford a bright orange solid in essentially quantitative yield. The elemental analysis and mass spectrum of this solid product both indicate that it is the desired pyridylmalononitrile derivative (168). However the remainder of its spectroscopic data were at odds with the structure (168) for this orange solid. In particular the ^{1}H n.m.r spectrum of this compound shows a broad singlet resonance at δ_H = 10.2 ppm intergrating for one proton which is completely removed on addition of deuterium oxide while the product's ^{13}C n.m.r spectrum exhibits a quaternary carbon resonance at δ_C = 40.7 ppm with no resonance attributable to an alkyl C-H carbon atom. This evidence, together with the presence of two very strong absorbtions at 2211 and 2160 cm^{-1} in the i.r. spectrum of the product indicative of a conjugated dicyano grouping, led to its formulation as the enamine strucure (171) with no evidence, at least in hexadeuterio dimethylsulphoxide solution, for the presence of tautomer (168). It was therefore

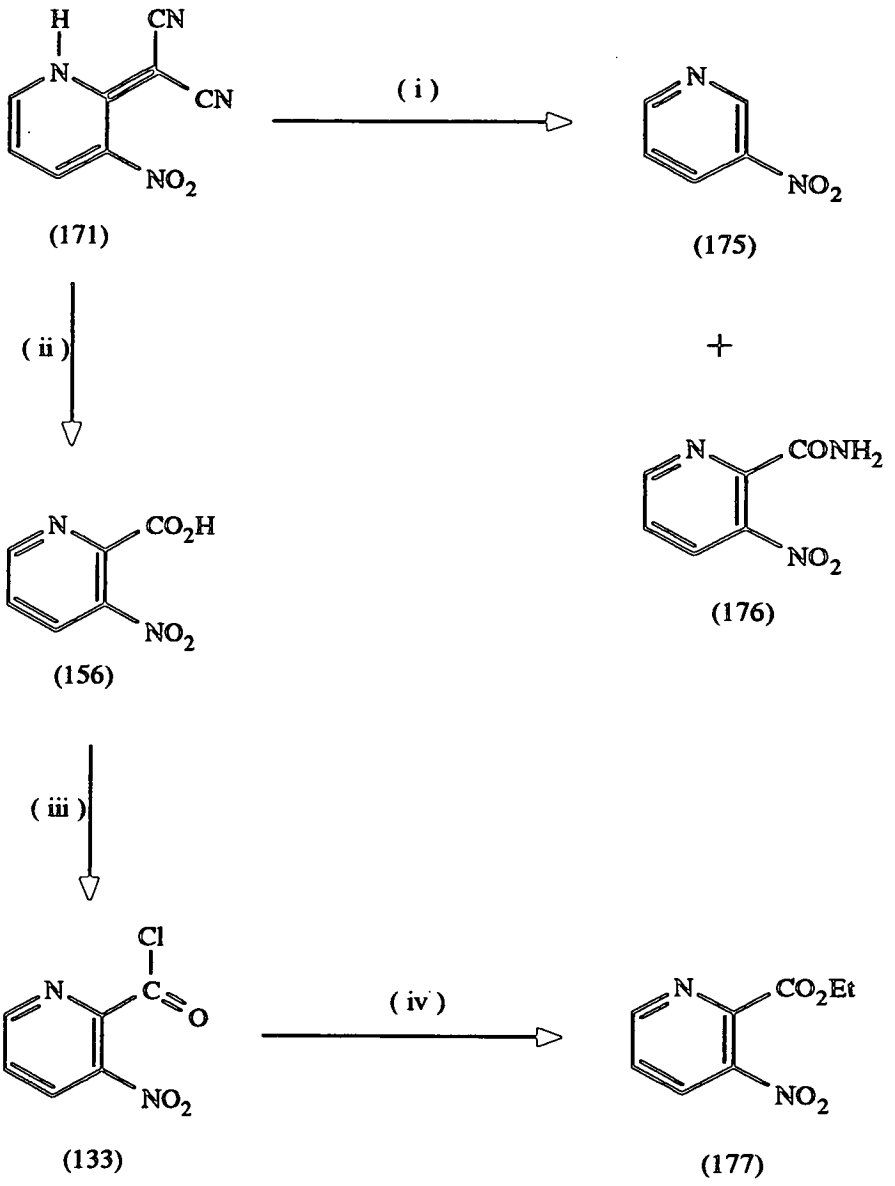


(i) $CH_2(CN)_2$, NaH, DMF, room temp.
(ii) MeI, NaH, DMF, room temp.
(iii) 30% H_2O_2, AcOH, 50°.

Scheme 50

hoped that methylation of the dicyano compound (171) would be likely to afford at least some of the *N*-methyl derivative thereby fixing the enamine structure thus allowing its oxidation to be studied. However, the reaction of the pyridylmalononitrile derivative (171) with sodium hydride followed by methyl iodide gave a monomethyl derivative whose spectroscopic data, in particular the lack of cyano absorbtion in its i.r. spectrum suggesting the presence of non-conjugated cyano groups, indicates that *C*-methylation has exclusively taken place to afford the undesired methyl derivative (172).

The oxidation of the pyridylmalononitrile derivative (171) by peracetic acid was next investigated but the only product which was isolated was a modest yield (39%) of the known[76] compound 3-nitropyridine *N*-oxide (174). This product presumably arisies from the decarboxylation of the initially formed 3-nitropicolinic acid *N*-oxide (173) a process which has been reported as being exceptionally facile.[76] Although initially disappointing, this result is also encouraging as it does indicate that the desired picolinic acid derivative has been formed and that its further *N*-oxidation is then causing the unwanted decarboxylation reaction to occur. Therefore in an attempt to prevent this *N*-oxidation (Scheme 51) the pyridylmalononitrile (171) was treated with alkaline hydrogen peroxide solution, conditions which should not cause *N*-oxidation. A vigorous exothermic reaction did occur but the only products which were ultimately isolated in low yield from this reaction were the known[73,77] compounds 3-nitropyridine (175) (16%) and 3-nitropyridine-2-carboxamide (176) (2%) these products presumably being derived from the initially formed 3-nitropicolinic acid (156). 3-Nitropicolinic acid (156) is known to readily decarboxylate in aqueous solution[71] although its anion is reported to be very stable towards decarboxylation but is said to undergo "some reaction other than decarboxylation" on warming in aqueous solution.[72] The amide (176) is presumably being produced by the reaction of 3-nitropicolinic acid (156) with ammonia which may have been liberated through hydrolysis of one of the many cyanide containing species in the reaction mixture.



(i) 30% H_2O_2 aqu., 1M NaOH aqu., 60°.
(ii) 30% H_2O_2 aqu., 1M NaOH aqu., 40°.
(iii) $SOCl_2$, reflux.
(iv) EtOH, room temp.

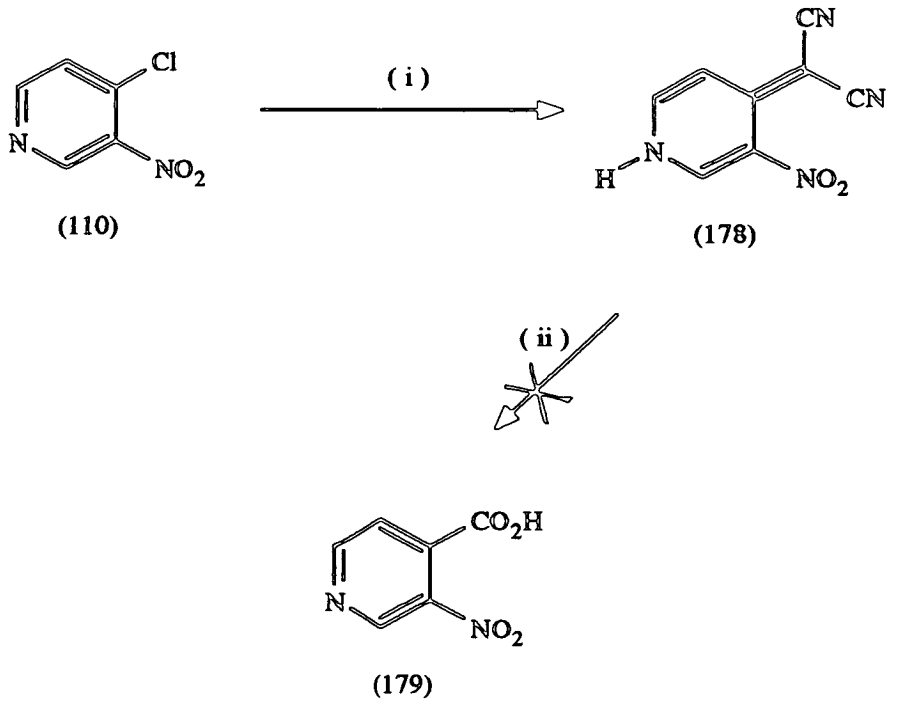
Scheme 51

In an attempt to prevent the presumably thermally induced decarboxylation reaction the oxidation of the pyridylmalononitrile derivative (171) by alkaline hydrogen peroxide was performed at 0-5°. However these conditions completely inhibited any reaction and resulted in only a good recovery of the unreacted starting material. On the other hand by allowing the exotherm of this oxidation reaction to warm the reaction mixture to 40° and then holding the temperature there by application of a cooling bath when necessary, good yields of the desired 3-nitropicolinic acid (156) could be successfully obtained. It was additionally pleasing to note that this oxidation reaction was reasonably reproducible and, in several runs on a 0.1 molar scale, the yield of 3-nitropicolinic acid (156) varied between, at best, 73% and, at worst, 51%.

The picolinic acid (156) was further characterised as its ethyl ester (177) which was obtained in excellent overall yield by first conversion into the known[75] unstable acid chloride (133) and then reaction of the latter with ethanol.

An attempt was then made to extend this new methodology for the preparation of arylcarboxylic acids to the synthesis (Scheme 52) of 3-nitroisonicotinic acid (179). To this end, 4-chloro-3-nitropyridine (110) was treated with the anion of malononitrile and afforded a good yield (59%) of the desired nitropyridylmalononitrile derivative (178) whose spectroscopic data suggest that it exists as the enamine tautomeric form as shown. Unfortunately, the reaction of (178) with alkaline hydrogen peroxide proved to be unsuccessful with no exothermic process occurring and only a good recovery of starting material being isolated. In an attempt to promote the alkaline hydrogen peroxide mediated oxidation of (178) the reaction was conducted at 40° but again gave only a good yield of unreacted starting material. In the light of these results, further attempts to oxidise the dicyano derivative (178) were not undertaken and the reasons for the failure of (178) to undergo oxidation remain unclear at present.

Since large quantities of the hitherto inaccesible 3-nitropicolinic acid (156) were now readily available it was considered worthwhile to undertake some preliminary studies into its use in heterocyclic synthesis. Thus (Scheme 53), it was of



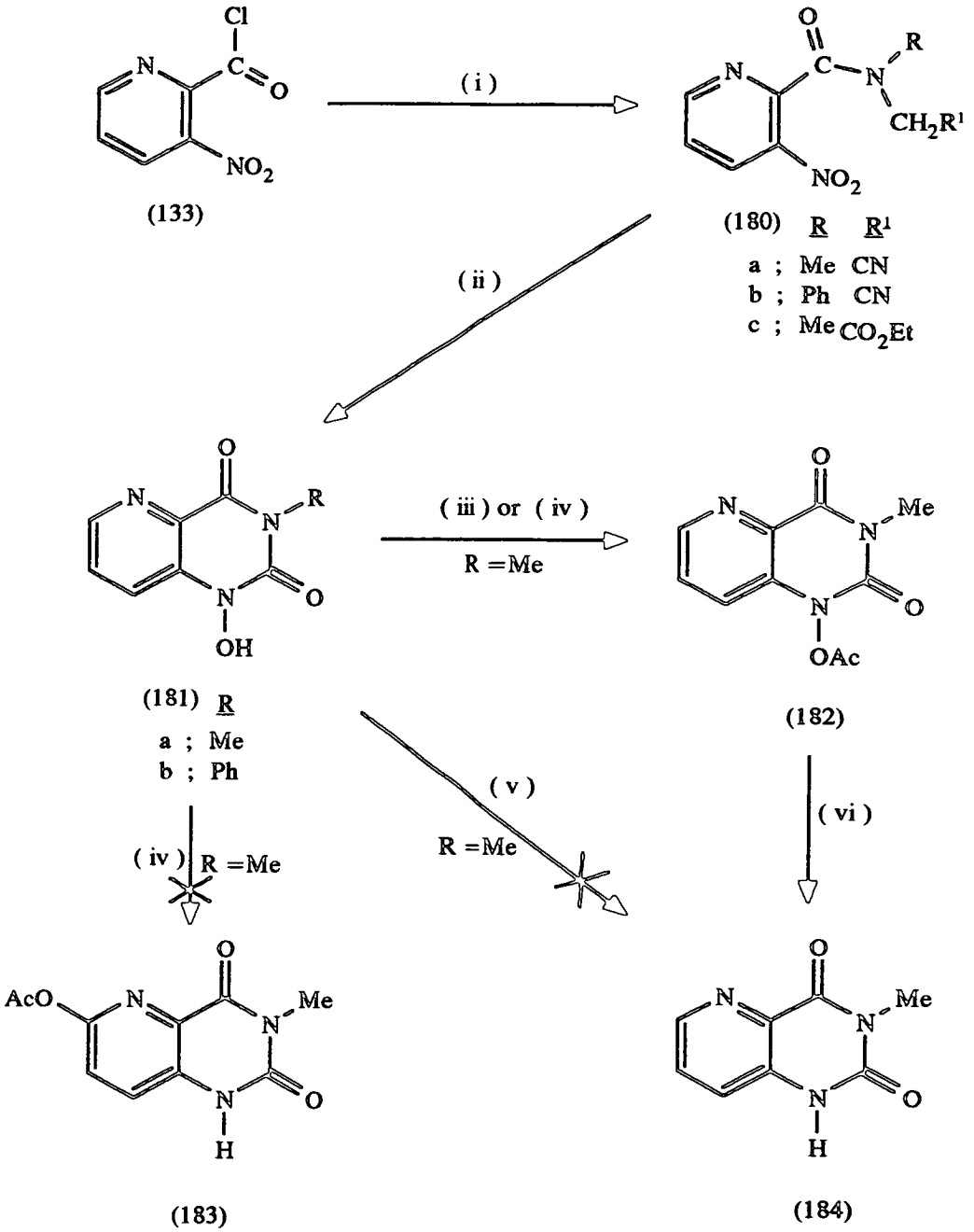
(i) $CH_2(CN)_2$, NaH, DMF, room temp.

(ii) 30% H_2O_2 aqu., 1M NaOH aqu., 40°.

Scheme 52

interest to apply methodology which had been previously reported for the synthesis of 1-hydroxyquinazoline-2,4-diones[78] to the synthesis of the previously unknown 1-hydroxy derivatives of pyrido[3,2-d]pyrimidine-2,4-diones (181). To this end, 3-nitropicolinic acid chloride (133) was treated with methylaminoacetonitrile hydrochloride in the presence of sodium acetate and afforded a good yield of the nitropyridinecarboxamide derivative (180a) whose elemental analysis and spectroscopic data are all in agreement with the assigned structure. An interesting feature of the ^1H n.m.r spectrum of (180a) is that there are two resonances each for the methylene protons (at $\delta_H = 4.7$ and 4.5 ppm) and for the methyl protons (at $\delta_H =$ 2.9 and 3.3 ppm) both in the approximate ratio of 2.6 : 1. It is believed that this phenomenon is due to the existence of two configurational isomers of (180a) which arise due to restricted rotation around the amide bond. This is substantiated by the fact that, in a variable temperature n.m.r. experiment, the two resonances for the methylene and those for the methyl protons independently coalesce at approximately 71°C to give only two resonances at $\delta_H = 4.6$ ppm and $\delta_H = 3.0$ ppm respectively.

It was gratifying to find that treatment of the nitropyridinecarboxamide derivative (180a) with sodium ethoxide in refluxing ethanol afforded a cream solid in 52% yield whose i.r. spectrum exhibits a very broad absorbtion between 3000 and 2000 cm^{-1} and which gives a deep red colour with ethanolic ferric chloride, features which indicate a cyclic hydroxamic acid structure for this solid product. The remainder of the product's spectroscopic data and its elemental analysis all verify that it is the expected 1-hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4-dione (181a). This heterocycle formed an *N*-acetoxy derivative (182) on brief warming in acetic anhydride solution whose structure is characterised by the high frequency carbonyl absorbtion at 1810 cm^{-1} in its i.r. spectrum. However (181a) could not be reduced by sodium dithionite to the parent heterocycle (184). On the other hand the latter compound was obtained by the catalytic hydrogenolysis of the *N*-acetoxy derivative (182), all of this chemical evidence supporting the original *N*-hydroxy structure (181a). Since the



(i) $RNHCH_2R^1$, NaOAc, AcOH, room temp.
(ii) NaOEt, EtOH, reflux.
(iii) Ac_2O, 100°.
(iv) Ac_2O, reflux.
(v) $Na_2S_2O_4$, 2M NaOH aqu., reflux.
(vi) H_2, Pd-C, DMF, room temp.

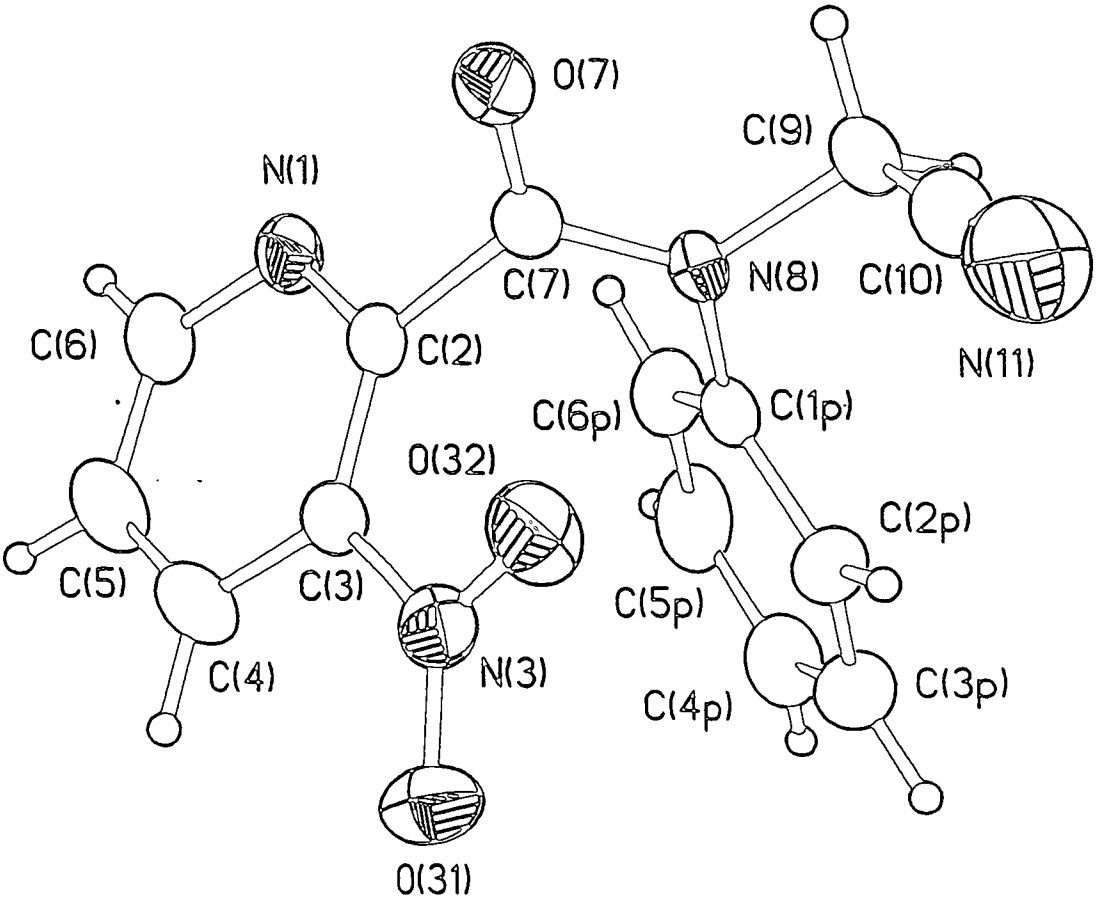
Scheme 53

sodium ethoxide-catalysed cyclisation of the nitropyridylcarboxamide (180a) gave only a moderate yield of cyclised product alternative conditions were sought for this transformation. Treatment of the nitropyridinecarboxamide (180a) with ethanolic sodium ethoxide at room temperature gave no identifiable products whereas the use of potassium hydroxide in ethanol or sodium hydride in 1,2-dimethoxyethane gave only low yields (26% and 31% respectively) of the pyridopyrimidine derivative (181a). No further attempts to optimise the efficiency of the transformation [(180a) → (181a)] were made.

In an analogous procedure to that used for the synthesis of the methyl derivative (180a), the acid chloride (133) was treated with anilinoacetonitrile to afford the phenylcarboxamide derivative (180b) in 50% yield. However in contrast to the methyl derivative (180a), the ^{1}H n.m.r. spectrum of the phenyl derivative (180b) in hexadeuterio dimethylsulphoxide solution shows the existence of only one conformational isomer. It is conceivable that this is due to the bulky phenyl group in (180b) resulting in only one stable conformer. Gratifyingly the phenylcarboxamide derivative (180b) crystallised as large diamond shaped crystals which were of suitable quality for single crystal X-ray diffraction analysis (see Figure 2 and Tables 6 and 7). The structure so demonstrated seems to indicate that there is some interaction between the π-electrons of the pyridine and phenyl rings in (180b) which may stabilise this structure and thus accounting for the existence of only one stable conformer of (180b).

Treatment of the phenylcarboxamide derivative (180b) with a solution of sodium ethoxide in refluxing ethanol resulted in the formation in low yield (26%) of the desired 1-hydroxy-3-phenylpyridopyrimidine derivative (181b) which gave a characteristic deep red colouration with ethanolic ferric chloride. However no further attempt was made to improve the yield of this heterocyclisation reaction.

The reaction of the acid chloride (133) with *N*-methyl glycine ethyl ester was also examined and this gave in good yield the desired carboxamide derivative (180c). The ^{1}H n.m.r. spectrum of the ester (180c), as for the analogous cyano derivative


O(7)
C(9)
N(1)
C(7)
N(8)
C(10)
C(6)
C(2)
N(11)
C(6p)
C(1p)
O(32)
C(2p)
C(5)
C(3)
C(5p)
C(4)
N(3)
C(4p)
C(3p)
O(31)

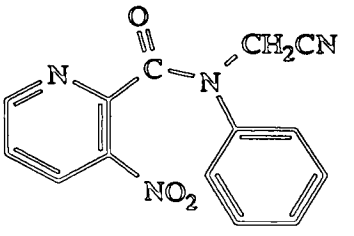

O
C
N
CH2CN
N
NO2

Figure 2

X-Ray Diffraction Data for 3-Nitropyridine-2-(*N*-cyanomethyl-*N*-phenyl)carboxamide (180b)

Table 6 : Bond Lengths (Angstroms) with Standard Deviations

N(1) - C(2)	1.341 (2)	N(1) - C(6)	1.332 (3)
C(2) - C(3)	1.375 (3)	C(2) - C(7)	1.514 (2)
C(3) - N(4)	1.465 (2)	C(3) - C(4)	1.374 (3)
N(3) - O(31)	1.217 (3)	N(3) - O(32)	1.220 (3)
C(4) - C(5)	1.368 (3)	C(5) - C(6)	1.365 (4)
C(7) - O(7)	1.216 (3)	C(7) - N(8)	1.349 (3)
N(8) - C(9)	1.460 (2)	N(8) - C(1P)	1.436 (3)
C(9) - C(10)	1.449 (3)	C(10) - N(11)	1.133 (3)
C(1P) - C(2P)	1.377 (3)	C(1P) - C(6P)	1.369 (3)
C(2P) - C(3P)	1.371 (4)	C(3P) - C(4P)	1.355 (3)
C(4P) - C(5P)	1.374 (4)	C(5P) - C(6P)	1.382 (4)

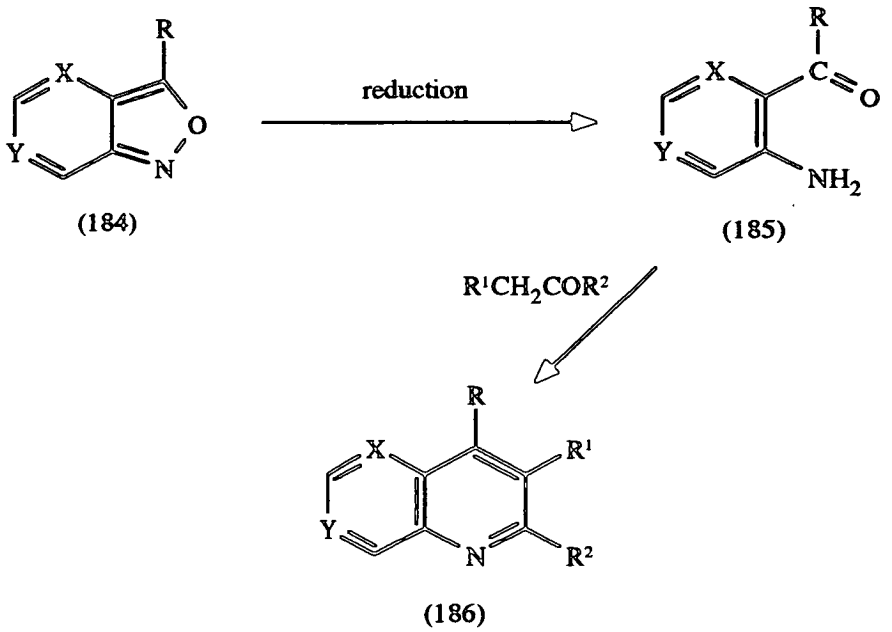
Table 7 : Bond Angles (Degrees) with Standard Deviations

C(2) - N(1) - C(6)	117.7 (2)	N(1) - C(2) - C(3)	120.9 (2)
N(1) - C(2) - C(7)	113.0 (2)	C(3) - C(2) - C(7)	126.0 (1)
C(2) - C(3) - N(3)	120.3 (2)	C(2) - C(3) - C(4)	120.8 (2)
N(3) - C(3) - C(4)	118.9 (2)	C(3) - N(3) - O(31)	118.0 (2)
C(3) - N(3) - O(32)	117.8 (2)	O(31) - N(3) - O(32)	124.2 (2)
C(3) - C(4) - C(5)	118.0 (2)	C(4) - C(5) - C(6)	118.6 (2)
N(1) - C(6) - C(5)	124.0 (2)	C(2) - C(7) - O(7)	120.2 (2)
C(2) - C(7) - N(8)	116.6 (2)	O(7) - C(7) - N(8)	123.1 (2)
C(7) - N(8) - C(9)	117.6 (2)	C(7) - N(8) - C(1P)	123.3 (1)
C(9) - N(8) - C(1P)	119.0 (2)	N(8) - C(9) - C(10)	112.1 (2)
C(9) - C(10) - N(11)	179.3 (3)	N(8) - C(1P) - C(2P)	120.1 (2)
N(8) - C(1P) - C(6P)	119.6 (2)	C(2P) - C(1P) - C(6P)	120.3 (2)
C(1P) - C(2P) - C(3P)	119.8 (2)	C(2P) - C(3P) - C(4P)	120.4 (2)
C(3P) - C(4P) - C(5P)	120.1 (3)	C(4P) - C(5P) - C(6P)	120.2 (2)
C(1P) - C(6P) - C(5P)	119.2 (2)		

(180a), shows the existence of two configurational isomers in deuteriochloroform solution. However an attempt to demonstrate the equilibration of these using ^{1}H n.m.r. spectroscopy was not undertaken. Unfortunately the attempted sodium ethoxide catalysed cyclisation of the ester (180c) gave only intractable mixtures of products and so investigations on the cyclisation of this derivative were not pursued further.

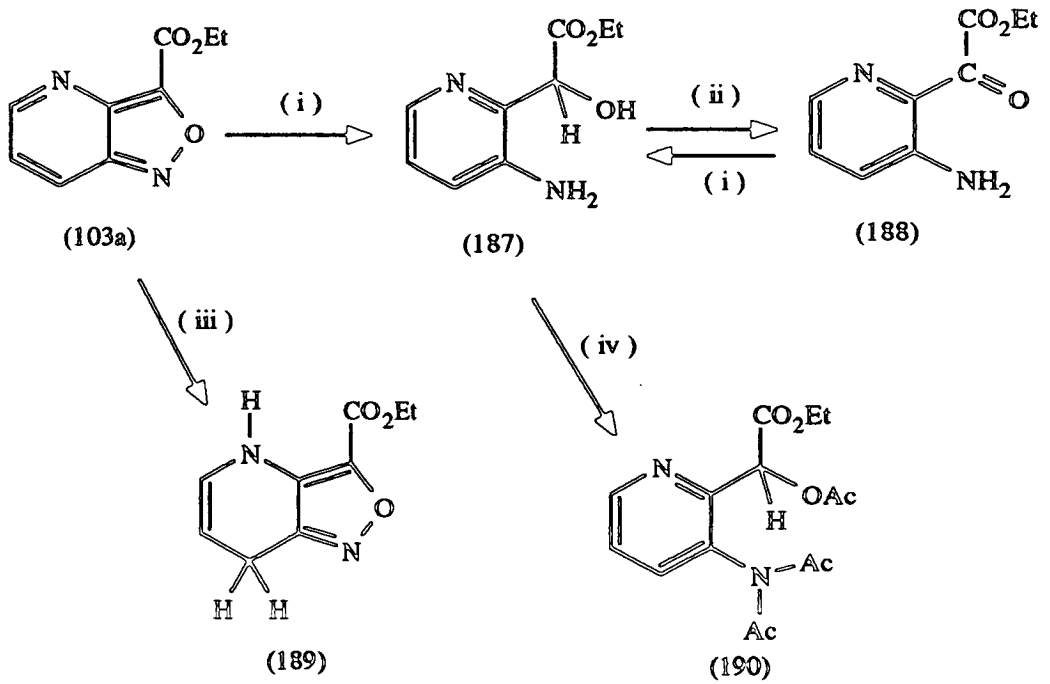
It was deemed of interest at this juncture to study the behaviour of the novel 1-hydroxypyridopyrimidines (181a) on strong heating with acetic anhydride in the hope that it might undergo rearrangement to the 6-acetoxypyridopyrimidine derivative (183). Similar rearrangements are known to occur in quinazoline[79,80] and quinoxaline derivatives.[81,82,83] However on prolonged heating of the 1-hydroxypyridopyrimidine derivative (180a) under reflux in acetic anhydride solution only a high yield of the *N*-acetoxy derivative (182) was obtained.

Further studies on the synthesis and reactivity of the novel pyridopyrimidine derivatives (181) were curtailed at this point due to time limitations.



	X	Y
a ;	N	CH
b ;	CH	N

Scheme 54



(i) H_2, Pd-C, EtOAc, room temp.

(ii) MnO_2, MeCN, room temp.

(iii) $NaBH_4$, dioxane, water, room temp.

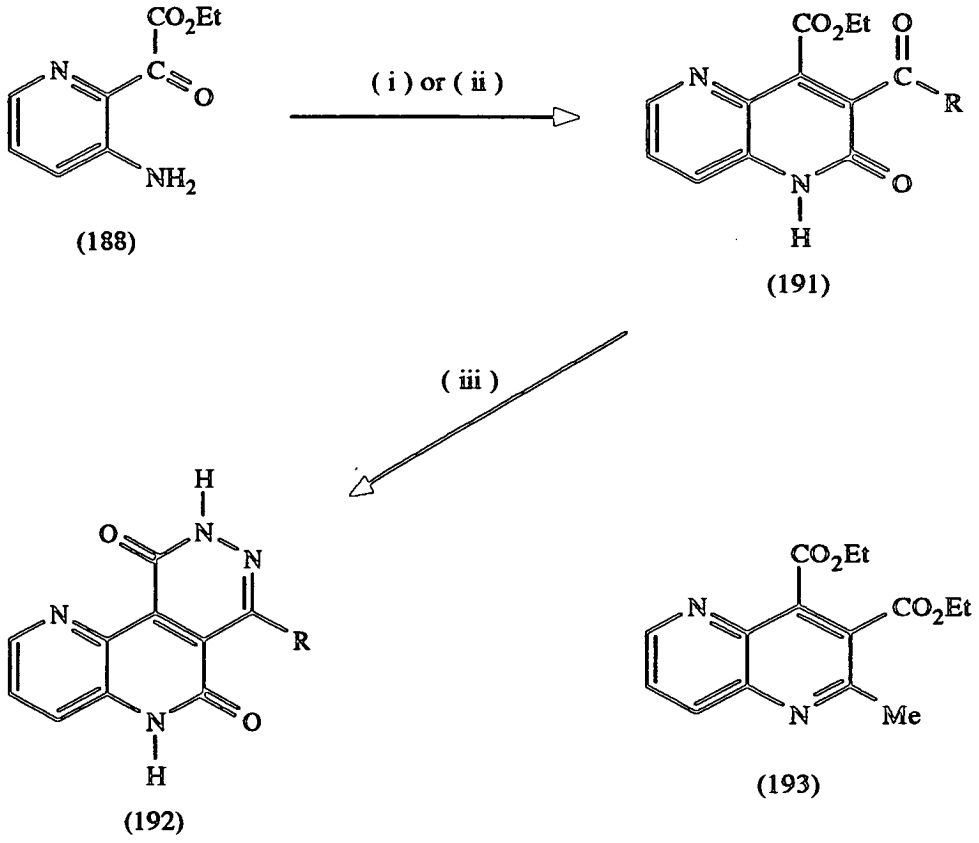
(iv) Ac_2O, reflux.

Scheme 55

2.5 : Studies on New Syntheses of 1,5- and 1,7-Napthyridine Derivatives

Ever since Friedlander prepared quinoline over one hundred years ago[84] by the condensation of 2-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide, the reaction of substituted 2-aminoacyl benzenes with carbonyl compounds containing an α-methylene group to afford quinolines has been extensively investigated.[85] The Friedlander synthesis has considerable advantage over alternative quinoline syntheses such as the Skraup synthesis,[86,87] the Combes synthesis[88] or the Doebner-von Miller synthesis[89] in that for the former case the position of annulation is fixed whereas in the latter syntheses, which utilise anilines as starting materials, isomer formation may take place by ring closure to either position *ortho* to the amino group. However the Friedlander synthesis does have the disadvantage that the requisite substituted 2-aminoacyl aromatic or heteroaromatic precursors are not readily available, a feature which was previously discussed in Chapter 2, Section 2.1 of this thesis. It was therefore of obvious interest (Scheme 54) to exploit the new isoxazolopyridine derivatives (184) which had been already prepared during the present studies for the synthesis of functionalised 1,5- and 1,7-napthyridine derivatives[67,90] (186) through their reduction to the 2-aminoacyl pyridines (185) followed by annulation in the manner of the Friedlander synthesis.

The Friedlander synthesis of napthyridines has been limited in the past to only a few examples all of which have utilised *ortho*-aminopyridinecarboxaldehydes as starting materials.[38,41,42,85] Investigations into the expansion of the scope of the Friedlander synthesis of napthyridines is therefore warranted. With this aim in mind (Scheme 55) the isoxazolopyridine (103a) was hydrogenated over a palladium catalyst in an attempt to obtain the aminopyridyl ketone (188). However, it was found that reduction of the isoxazolopyridine (103a) was very rapid and that two equivalents of hydrogen were absorbed to give the aminopyridyl hydroxymethyl derivative (187) which was further characterised by conversion into its triacetate derivative (190).



(i) EtO_2CCH_2COR, xylene, reflux.

(ii) EtO_2CCH_2COR, diglyme, reflux.

(iii) $NH_2NH_2 \cdot H_2O$, EtOH, reflux.

R

a ; Me

b ; Ph

c ; CO_2Et

d ; CH_2CO_2Et

Scheme 56

Similar examples of the over-reduction of 2,1-benzisoxazole derivatives to give aminoaryl hydroxymethyl or aminoaryl methylene derivatives are known.[91] Alternative efforts to reduce the isoxazolopyridine (103a) with either sodium dithionite or titanium trichloride both failed to give the aminopyridyl ketone (188) but the reduction of the isoxazolopyridine (103a) with sodium borohydride did afford a low yield (18%) of a tan solid whose elemental analysis and mass spectrum both indicate that a dihydro derivative of the isoxazolopyridine (103a) was formed. However, the ^{1}H n.m.r. spectrum of this dihydro derivative suggests that the pyridine ring has been reduced and examination of the multiplicities for the proton resonances of this compound led to its formulation as the 4,7-dihydroisoxazolopyridine derivative (189). This compound presumably arises from the Michael addition of hydride ion to the $\alpha,\beta-$unsaturated imine system of the isoxazolopyridine (103a).

In the light of these results it was gratifying to find that the aminopyridyl hydroxymethyl derivative (187) could be oxidised in excellent yield using manganese dioxide to give the desired aminopyridyl ketone (188). This process was found to be reversible as demonstrated by the catalytic hydrogenation of the ketone (188) to afford the alcohol (187) in good yield.

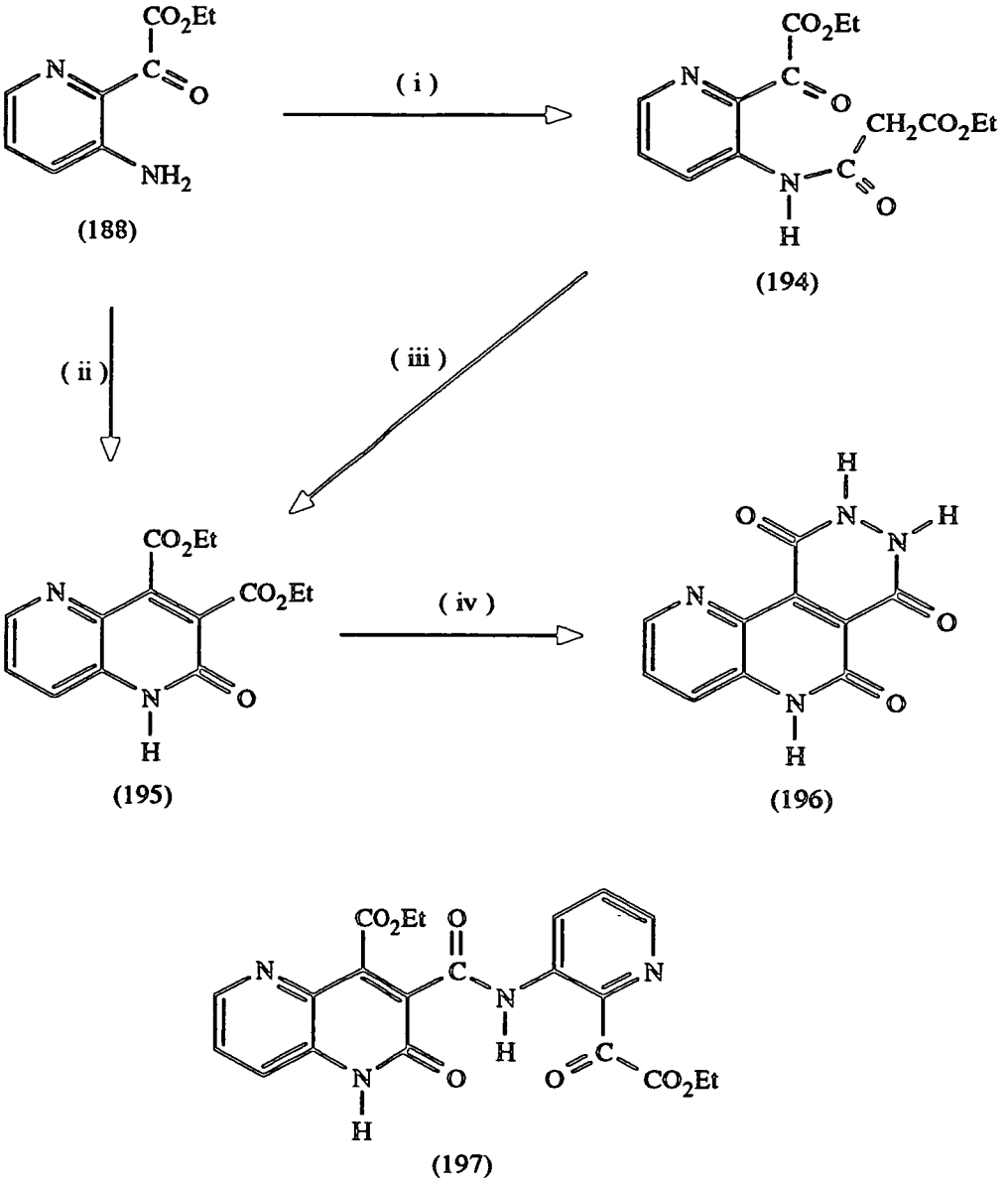
With the aminopyridyl ketone (188) in hand attention was next turned to its annulation to afford 1,5-napthyridine derivatives. There are many ways to carry out the Friedlander synthesis[84] using either acid or base catalysis or under purely thermal conditions. Also a variety of different α-methylene carbonyl substrates have been employed.[84] Initially the thermal condensation of the aminopyridyl ketone (188) with β-ketoesters was studied (Scheme 56) and in this context a solution of the amine (188) and ethyl acetoacetate in xylene was heated under reflux. This reaction proved to be sluggish and required 22h for complete consumption of the amine (188) as shown by t.l.c. of the reaction mixture. Under these conditions only a low yield (29%) of the desired 3-acetyl-1,5-napthyridin-2-one derivative (191a) was formed. The lactam structure of the right hand ring (as drawn) in this product was clearly evident from the

characteristic broad absorbtion between 3100 and 2500 cm^{-1} in its i.r. spectrum.[92] The remainder of the material isolated from this reaction consisted only of a complex, inseperable mixture of products. The napthyridinone (191a) was also characterised by its reaction with hydrazine to afford the fused pyridazinone derivative (192a). In an attempt to improve the yield of the napthyridinone (191a), the amine (188) and ethyl acetoacetate were heated under reflux in the higher boiling solvent diglyme but these conditions gave only a disappointingly low yield (10%) of the desired product (191a). Since the condensation of the amine (188) with ethyl acetoacetate produces ethanol and water it was speculated that removal of these two by-products would facilitate this condensation reaction. This was indeed found to be the case since, when a xylene solution of the amine (188) and ethyl acetoacetate were heated under reflux with cycling of the solvent through a soxhlet extractor containing 5Å molecular sieves, a high yield (87%) of the desired 1,5-napthyridin-2-one derivative (191a) was produced after a reaction time of only 3h under these conditions. An experiment conducted in parallel with the previous one in which xylene was replaced with the higher boiling diglyme resulted in only a 26% yield of the desired napthyridinone (191a).

In an analogous fashion, ethyl benzoylacetate was condensed with the aminopyridyl ketone (188) in refluxing xylene in the presence of molecular sieves to give the 3-benzoyl-1,5-napthyridin-2-one derivative (191b) in 85% yield which also formed a pyridazinone derivative (192b) on reaction with hydrazine.

Diethyl 2-oxobutanedioate also readily condensed with the amine (188) under the same conditions used for the previous two β-ketoesters to give the 1,5-napthyridin-2-one derivative (191c) in good yield (75%) and this also formed a fused pyridazinone derivative (192c) on reaction with hydrazine. An attempt to similarly condense diethyl acetonedicarboxylate with the amine (188) unfortunately failed, this reaction leading only to the production of an unidentifiable, intractable solid.

In the three successful 1,5-napthyridin-2-one syntheses which have just been described the only identifiable products obtained were those derived from the



(197)

(i) EtO_2CCH_2COCl, benzene, reflux.

(ii) $(EtO_2C)_2CH_2$, xylene, mol. sieves 5A, reflux.

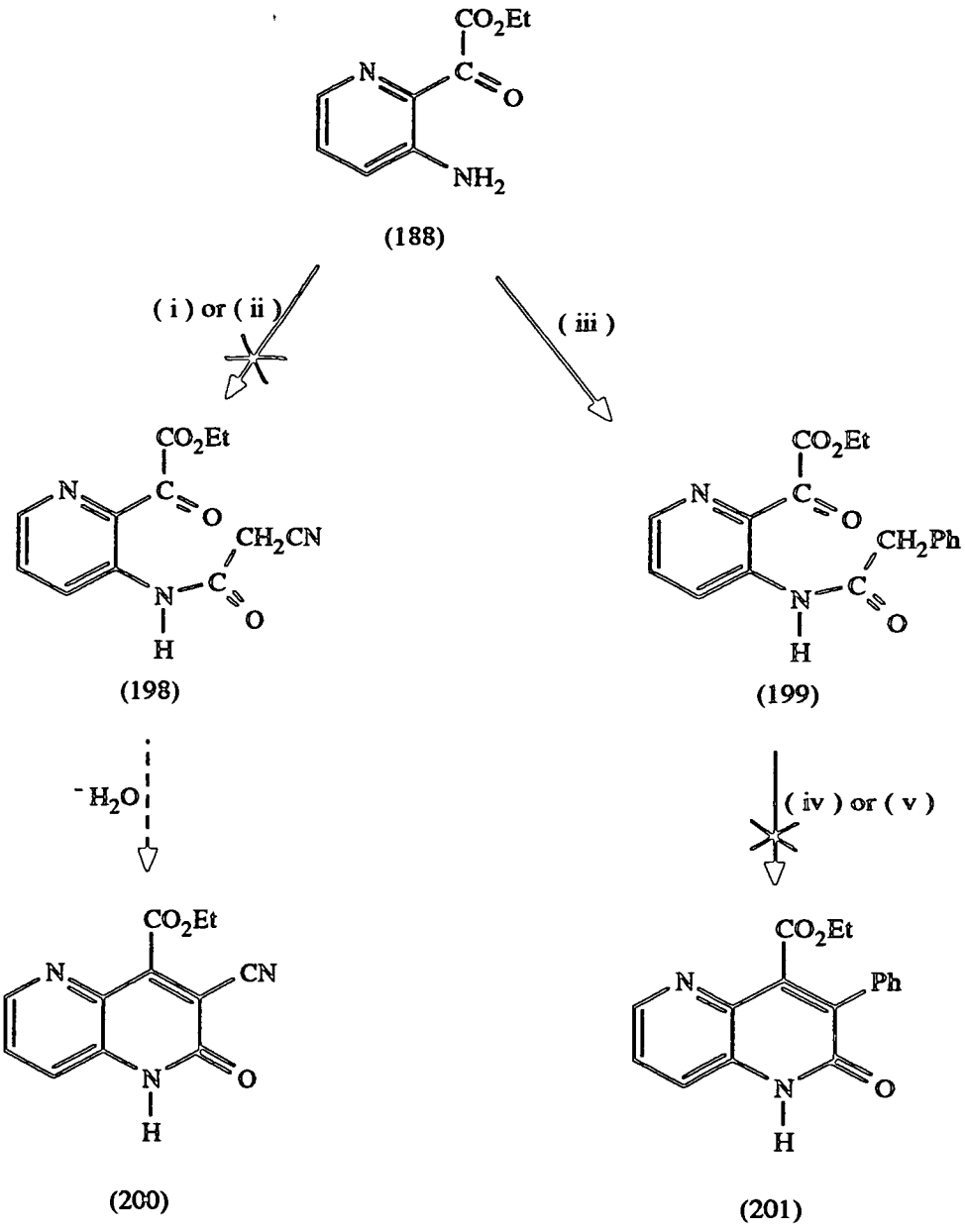
(iii) Et_3N, EtOH, reflux.

(iv) $NH_2NH_2 \cdot H_2O$, reflux.

Scheme 57

condensation of the amino group in (188) with the less electrophilic ester carbonyl group of the β-ketoester. This has been previously found to be the expected result from such uncatalysed, purely thermally-induced condensations.[93] In an attempt to synthesise the alternative condensation product (193), the aminopyridyl ketone (188) and ethyl acetoacetate were heated under reflux in acetic acid containing a catalytic amount of sulphuric acid, conditions under which 2-aminoaryl ketones are known to react with the more electrophilic keto group of β-ketoesters.[93] However, these conditions failed to yield any identifiable products as did the attempted condensation of the amine (188) with ethyl acetoacetate under the mildly basic conditions of heating under reflux with piperidine in glacial acetic acid. Further attempts to obtain the 1,5-napthyridine derivative (193) were not undertaken.

Next (Scheme 57) an attempt was made to condense the aminopyridyl ketone (188) with diethyl malonate in refluxing xylene solution using molecular sieves to remove the volatile by-products. Under these conditions the starting materials were completely consumed after 8h and two products were produced which were readily separable by flash-chromatography. The minor product (22%) was found to be the desired diethyl 1,5-napthyridin-2-one-3,4-dicarboxylate (195) the structure of which was in full agreement with its spectroscopic data and elemental analysis. An attempt to further characterise the diester (195) by hydrolysis to its diacid derivative using aqueous sodium hydroxide failed to give any recognisable products and the attempted conversion of the diester (195) into the tricyclic pyridazinone derivative (196) failed under the standard reaction conditions employed (hydrazine hydrate in refluxing ethanol). However the diester (195) did afford a high melting (>360°) solid derivative by heating under reflux in neat hydrazine hydrate solution which is formulated as the tricyclic pyridazinone derivative (196) on the basis of its spectroscopic data. Unfortunately the extremely insoluble nature of the solid product (196) made satisfactory purification impossible and therefore no acceptable elemental analysis for the derivative (196) could be obtained.



(i) $NCCH_2COCl$, benzene, reflux.

(ii) $NCCH_2COCl$, NaOAc, AcOH, room temp.

(iii) $PhCH_2COCl$, benzene, reflux.

(iv) Et_3N, EtOH, reflux.

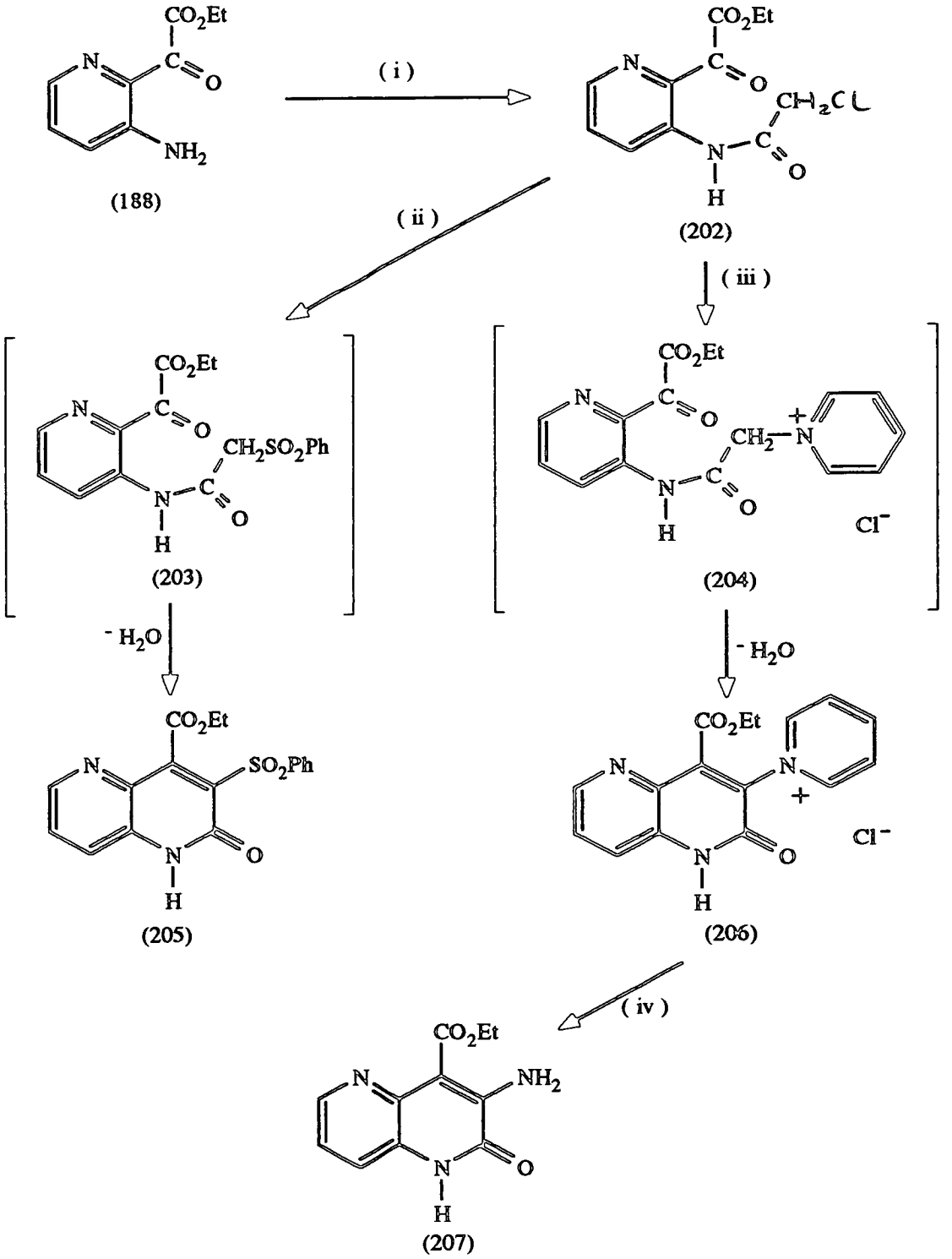
(v) NaOEt, EtOH, reflux.

Scheme 58

The major product from the condensation of the amine (188) with diethyl malonate, obtained in 49% yield, is assigned as the napthyridinone derivative (197) wherein a second molecule of the aminopyridyl ketone (188) has reacted with one of the ester groups of the 1,5-napthyridin-2-one (195). Although the 3-amido structure (197) is proposed (Scheme 57), the alternative 4-amido structure cannot be ruled out. However the former 3-amido isomer (197) is prefered in as much as that under similar reaction conditions to those which produced the isomer (197), the ethyl 3-acyl-1,5-napthyridin-2-one-4-carboxylates (191a-c) do not form any such amide products. This therefore suggests that a 4-ethoxycarbonyl substituent in a 1,5-napthyridin-2-one does not react thermally with an amine.

In view of the poor yield of the diester (195) obtained in the thermal condensation of the aminopyridyl ketone (188) with diethyl malonate an alternative method for the synthesis of the diester (195) was therefore sought. To this end the amine (188) was treated with ethyl malonyl chloride and gave the desired amide derivative (194) in excellent yield as an unstable brown oil. Attempted purification of the amide (194) by flash chromatography over silica fortuitously resulted in its dehydrative cyclisation to give the desired 1,5-napthyridin-2-one derivative (195) in high yield (85%). An attempt to carry out a more controlled cyclisation of the amide (194) by base-catalysed cyclisation using sodium ethoxide in refluxing ethanol led only to complete decomposition of the starting material. However it was pleasing to find that the 1,5-napthyridin-2-one derivative (195) could be obtained in reproducibly good yield by the triethylamine-catalysed cyclisation in refluxing ethanol of the crude amide (194).

An attempt (Scheme 58) to condense ethyl cyanoacetate with the aminopyridyl ketone (188) in refluxing xylene to hopefully give the 3-cyano-1,5-napthyridin-2-one (200) failed, giving only unreacted starting material (188). Also disappointing was the alternative procedure of condensing cyanoacetyl chloride with the aminopyridyl ketone



(i) $ClCH_2COCl$, toluene, reflux.

(ii) $PhSO_2Na$, EtOH, reflux.

(iii) pyridine, 100°.

(iv) piperidine, MeOH, reflux.

Scheme 60

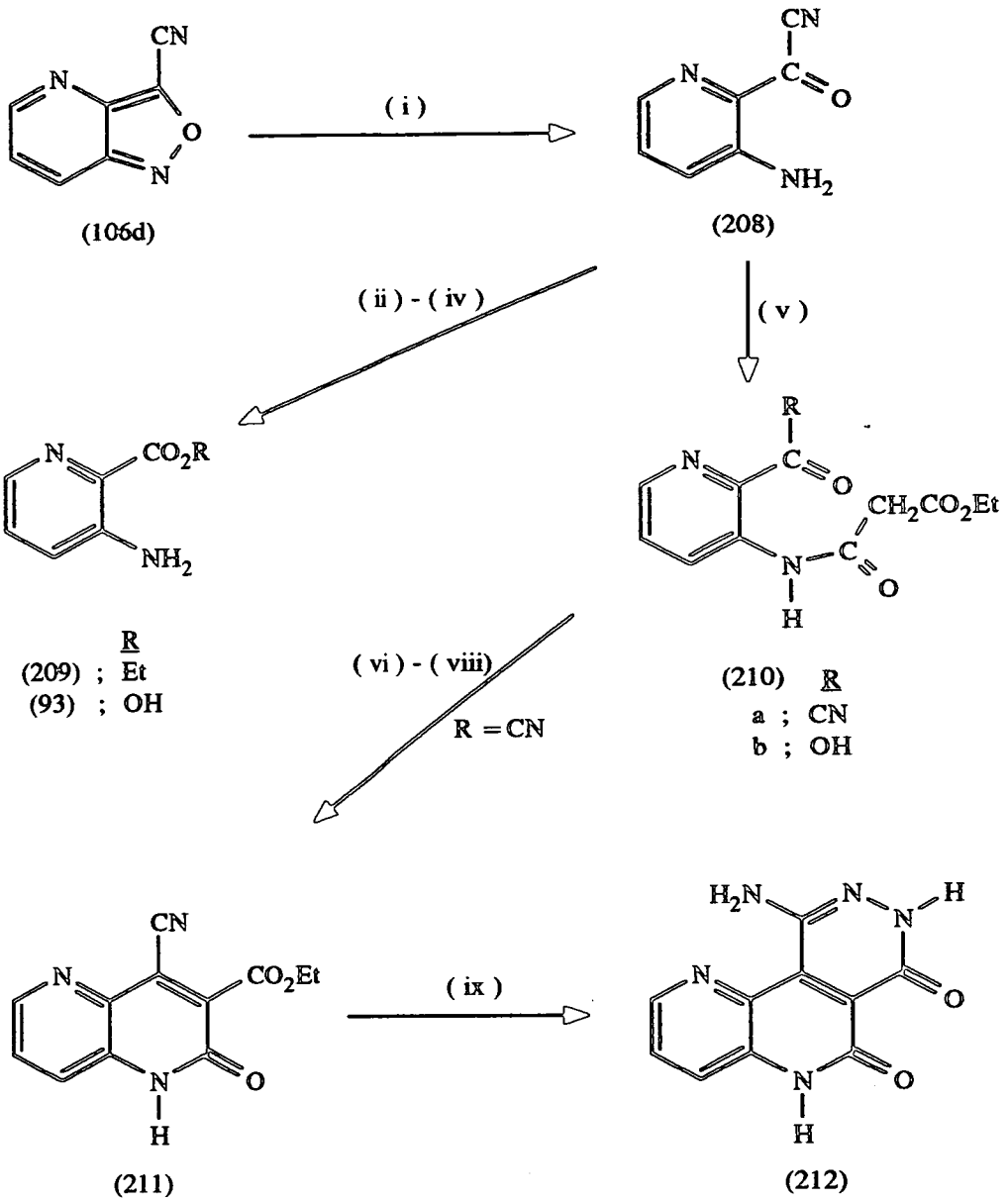
(188) which failed to afford the desired amide product (198) either in refluxing benzene solution or in 1,2-dimethoxyethane solution with catalysis by triethylamine.

Phenylacetyl chloride did react readily with the amine (188) to afford a good yield of the phenylacetamide derivative (199). However attempted base-catalysed cyclisation of (199) to hopefully afford the 3-phenyl-1,5-napthyridin-2-one (201) failed with either triethylamine or sodium ethoxide as catalysts, the former giving unreacted starting material while the latter resulted only in complete decomposition of the starting material. Further attempts to cyclise the phenylacetamide (199) were therefore not pursued.

The synthesis of 1,5-napthyridine derivatives containing *ortho*-amino carbonyl functionality was next investigated since the annulation of this type of compound would afford a variety of novel tricyclic heterocycles. In particular the construction of a fused pyrimidine ring onto such *ortho*-amino carbonyl napthyridines by the application of standard methodologies previously employed for the synthesis of quinazolines[107] would afford novel pyrimidonapthyridines of the type illustrated in Scheme 59. As well as being of interest purely as new heterocyclic ring systems,

Scheme 59

the type of compounds shown in Scheme 59 should have the ability to bind to DNA. A more detailed discussion of this subject will be delayed until Section 2.7 of this chapter as will details of the syntheses of the appropriate tricyclic heteroaromatics. With this in mind investigations were undertaken (Scheme 60) into the synthesis of the 3-amino-



(i) H_2, Pd-C, EtOAc, room temp
(ii) EtOH, reflux.
(iii) AcOH, water, reflux.
(iv) AcOH, water, room temp.
(v) EtO_2CCH_2COCl, benzene, reflux.
(vi) Et_3N, DME, reflux.
(vii) Et_3N, DME, room temp.
(viii) i-Pr_2NEt, DME, room temp.
(ix) $NH_2NH_2 \cdot H_2O$, EtOH, reflux.

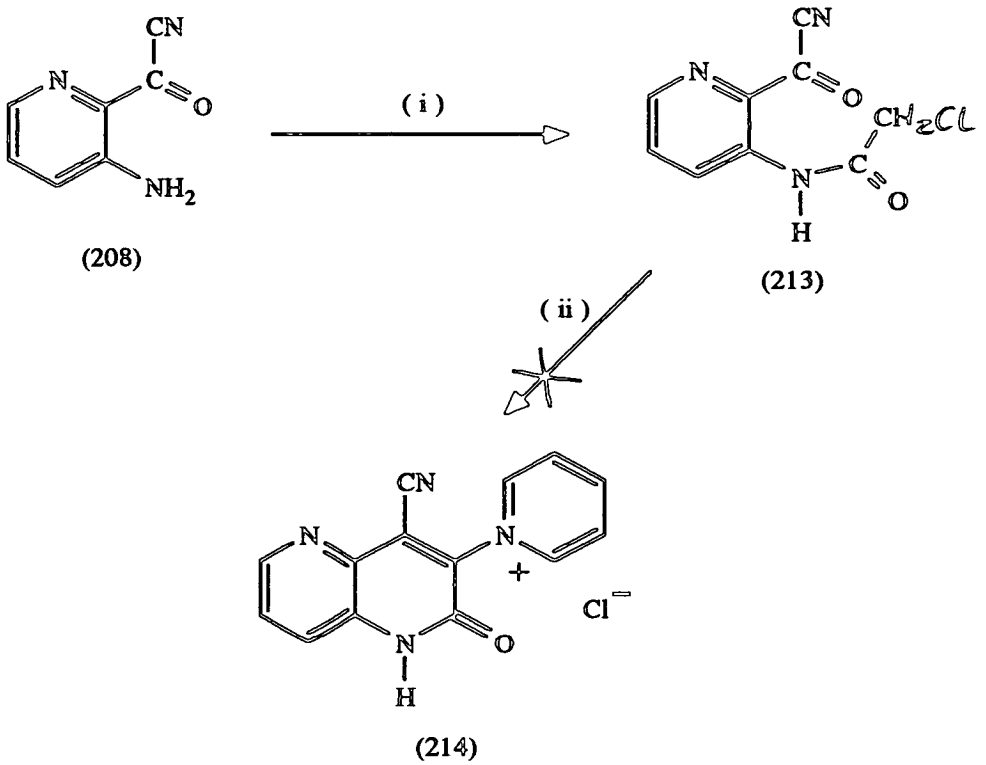
Scheme 61

1,5-napthyridin-2-one derivative (207). To begin with the aminopyridyl ketone (188) was chloroacetylated to give a high yield (86%) of the chloroacetamide (202). The reaction of (202) with sodium benzenesulphinate in dimethylformamide at 100° afforded the 3-benzenesulphonyl-1,5-napthyridin-2-one derivative (205) presumably via in situ cyclisation of of the initially formed benzenesulphonylacetamide derivative (203). It was planned to displace the benzenesulphonyl group from (205) with ammonia to give the 3-amino-1,5-napthyridin-2-one derivative (207) but this reaction was not investigated in the light of the successful synthesis of (207) which is described next.

The reaction of the chloroacetamide (202) with pyridine at 100° afforded a high yield of the pyridinium salt (206) presumably via cyclisation of an initially formed acyclic pyridinium species (204). Of most importance was the further transformation of this salt (206) in near quantitative yield into the 3-amino-1,5-napthridin-2-one derivative (207) by cleavage of the pyridinium ring with piperidine in refluxing methanol.[94] The *ortho*-amino ester (207) is a useful precursor of tricyclic heterocycles the synthesis of which are described later in this chapter (Section 2.7).

Next an attempt was made to prepare a 1,5-napthyridine-2,3,4-tricarboxylate derivative via the reaction of the aminopyridyl ketone (188) with dimethyl acetylenedicarboxylate.[95] However this reaction was unsuccessful giving only a good recovery of unreacted starting material (188).

Attention was next directed (Scheme 61) to the exploitation of the 3-cyanoisoxazolopyridine (10*b*d) in the synthesis of 1,5-napthyridine derivatives. In this context the isoxazolopyridine (10*b*d) was hydrogenated over a palladium catalyst and afforded an excellent yield of the aminopyridyl acyl cyanide (208) as a crystalline solid whose i.r. spectrum showed absorbtions at 2221 and 1648 cm^{-1} characteristic of an acyl cyanide.[96] The reactivity of the acyl cyanide (208) was exemplified by its hydrolysis in aqueous acetic acid solution either by heating under reflux or at room



(208)

(213)

(214)

(i) $ClCH_2COCl$, benzene, reflux.

(ii) pyridine, 100°.

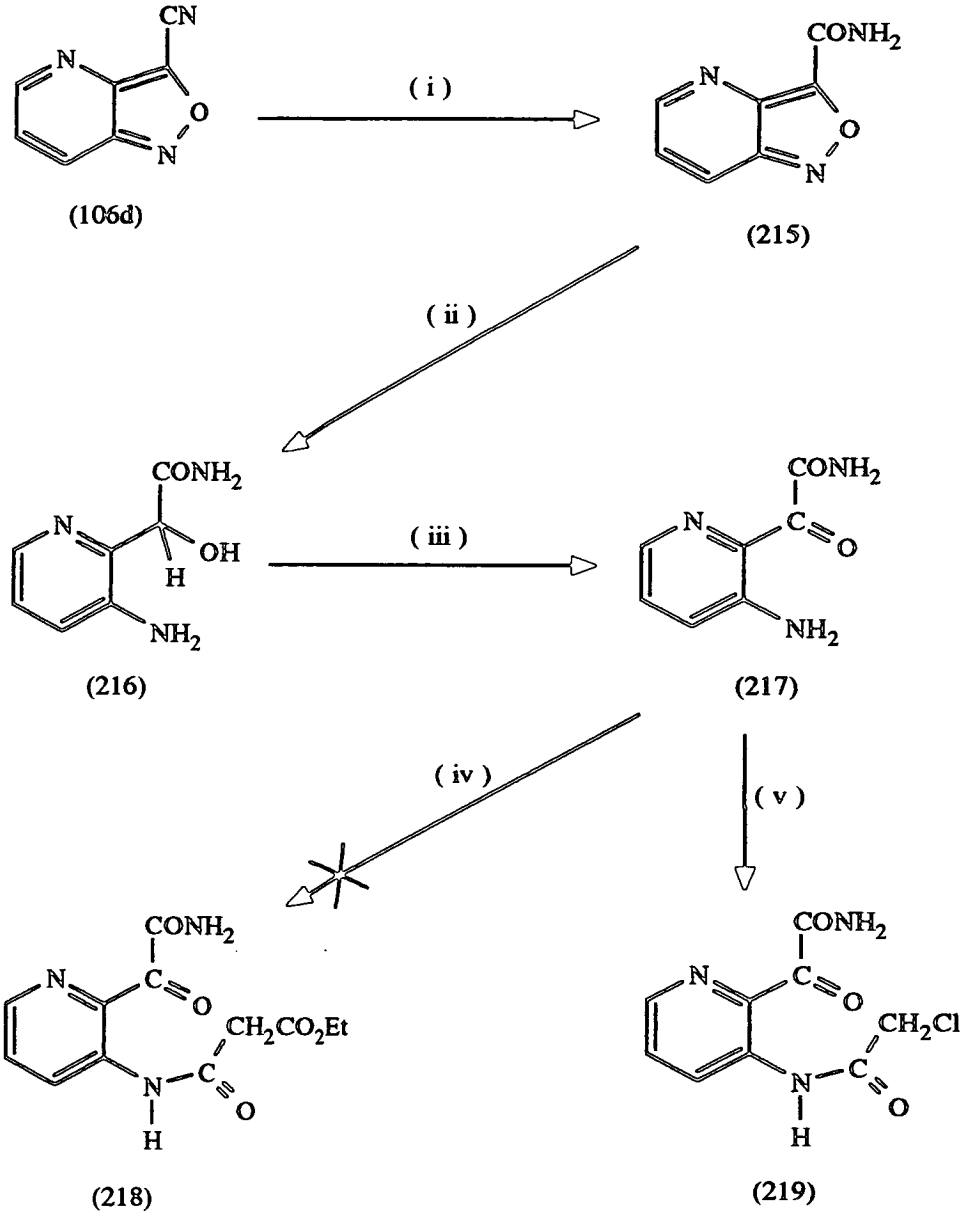
Scheme 62

temperature to give the known[40] 3-aminopicolinic acid (93) and also by its reaction with ethanol to afford a high yield of the ester derivative (209).

The reaction of the acyl cyanide (208) with ethyl malonyl chloride afforded a crude solid product whose i.r. spectrum suggests that it is the desired amide derivative (210a). However this compound proved to be very reactive and was quickly hydrolysed during the reaction work up, even on just washing the crude product with ethyl acetate in an attempt to remove any gumminess, to give the picolinic acid derivative (210b) in low yield (28%) as the only identifiable product. Therefore the crude amide derivative (210a) was used directly without further purification and thereby afforded a low yield (20%) of the 4-cyano-1,5-napthyridin-2-one derivative (211) on treatment with triethylamine in refluxing DME solution. This napthyridinone (211) was also characterised by its conversion into the high melting tricyclic pyridazinone derivative (212) on treatment with hydrazine. In attempts to improve the yield of the napthyridinone (211), the amide (210a) was treated with triethylamine in DME at room temperature to give a slightly improved (27%) yield of the napthyridinone (211). On the other hand catalysis of the transformation [(210a) → (211)] by diisopropylethylamine (Hünig's base) gave a lower yield (16%) of the desired product (211). Further optimisation of the efficiency of the cyclisation [(210a) → (211)] was not undertaken.

The reaction (Scheme 62) of the acyl cyanide (208) with chloroacetyl chloride in refluxing toluene solution failed to give any recognisable products while in refluxing benzene solution these reactants afforded a moderate yield (47%) of the expected chloroacetamide derivative (213) as an unstable tan solid. However the attempted reaction of (213) with pyridine to hopefully afford the 1,5-napthyridin-2-one derivative (214) was disappointing resulting only in the formation of intractable solids and gums.

Due to the inherent instability of the acyl cyanide derivatives under study and the low yields obtained in the reactions thereof, investigations on the annulation reactions of the aminopyridyl acyl cyanide (208) were discontinued at this point.



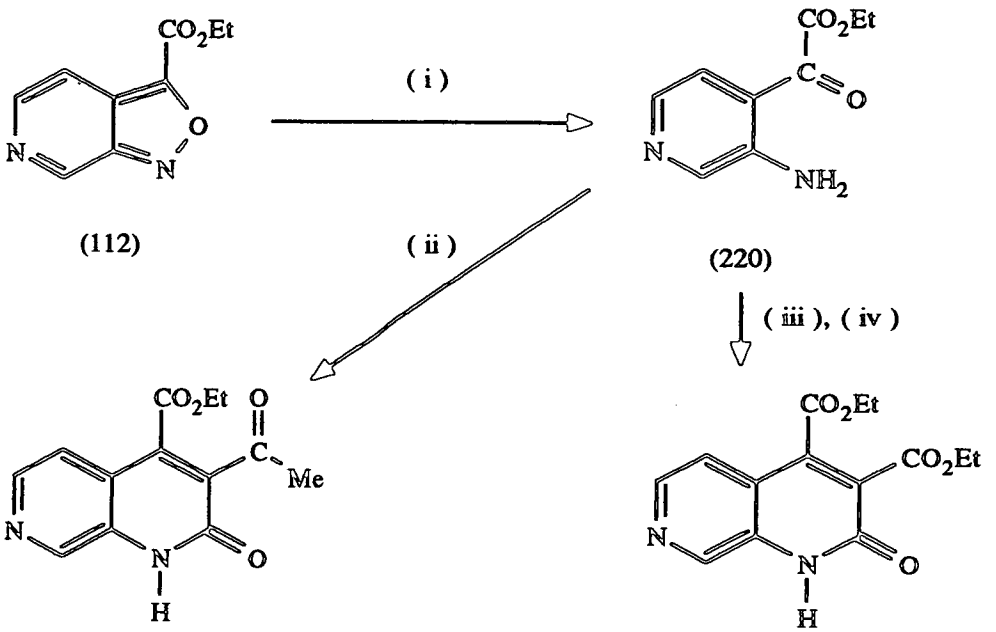
(i) H_2SO_4 conc., room temp.
(ii) H_2, Pd-C, DMF, room temp.
(iii) MnO_2, DMF, room temp.
(iv) EtO_2CCH_2COCl, benzene, reflux.
(v) $ClCH_2COCl$, toluene, reflux.

Scheme 63

Another approach to 1,5-napthyridine derivatives which was the subject of preliminary investigations (Scheme 63) was the annulation of the aminopyridyl glyoxamide (217). This compound was obtained in three steps starting with the hydrolysis of the 3-cyanoisoxazolopyridine (106d) to give the carboxamide derivative (215). The carboxamide (215) was then subjected to catalytic hydrogenation to afford the aminopyridyl hydroxymethyl derivative (216). Both of these reactions proceeded in high yield. The alcohol (216) was then oxidised by activated manganese dioxide to yield the aminopyridyl glyoxamide (217) in moderate yield (55%). However, attempts to acylate the aminopyridyl glyoxamide (217) proved to be disappointing. Treatment of the amine (217) with ethyl malonyl chloride gave no recognisable products while the reaction of (217) with chloroacetyl chloride gave only a low yield of the chloroacetamide derivative (219). Further studies on the annulation of the aminopyridyl glyoxamide (217) were not undertaken due to these disappointing initial results.

The extension of the new methodology under study to the synthesis of 1,7-napthyridine derivatives was next considered (Scheme 64) and in this respect the isoxazolopyridine derivative (112) was hydrogenated over a palladium catalyst. Since this reduction has to be performed on crude starting material (see Section 2.2) only a 50% yield of the desired aminopyridyl ketone (220) was obtained. The spectroscopic data for (220) were all in agreement with the assigned structure. However the aminopyridyl ketone (220) proves to be unstable on storage at room temperature and required storage at -20° to avoid significant decomposition. Due to this instability, no satisfactory elemental analysis for (220) could be obtained.

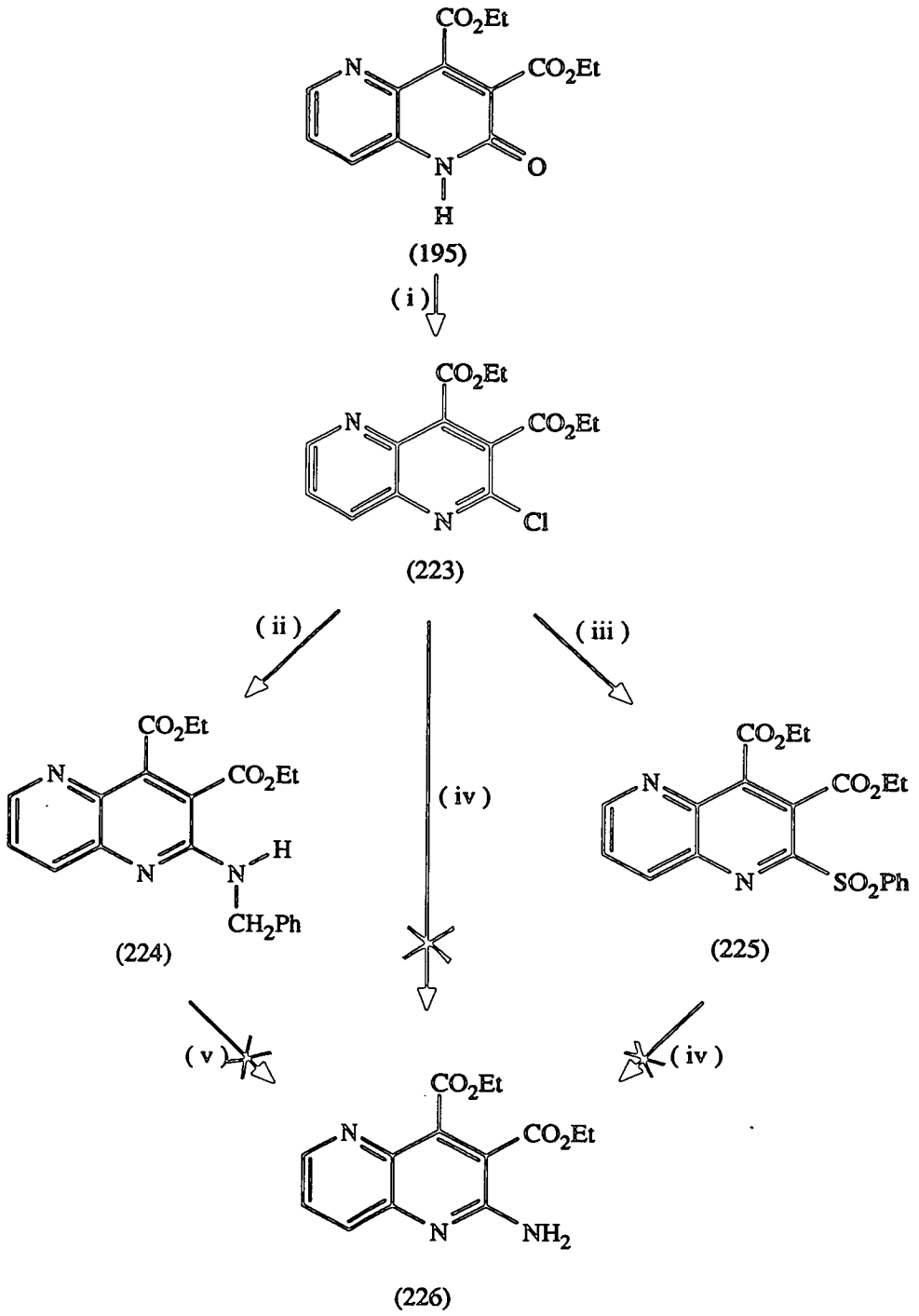
The condensation of ethyl acetoacetate with the amine (220) in refluxing xylene using molecular sieves to remove the volatile by-products afforded a good yield (63%) of the desired 3-acetyl-1,7-napthyridin-2-one derivative (221). The reaction of (220) with ethyl malonyl chloride in refluxing benzene afforded the hydrochloride of diethyl 1,7-napthyridin-2-one-3,4-dicarboxylate (222) in 58% yield. The free compound (222)



(i) H_2, Pd - C, EtOAc, room temp.
(ii) $MeCOCH_2CO_2Et$, xylene, reflux.
(iii) EtO_2CCH_2COCl, benzene, reflux.
(iv) NaOAc, water, room temp.

Scheme 64

was liberated from the hydrochloride on treatment of the latter with aqueous sodium acetate.



(i) $POCl_3$, $PhNMe_2$, reflux.

(ii) $PhCH_2NH_2$, EtOH, reflux.

(iii) $PhSO_2Na$, DMF, 100°.

(iv) NH_3, -78°.

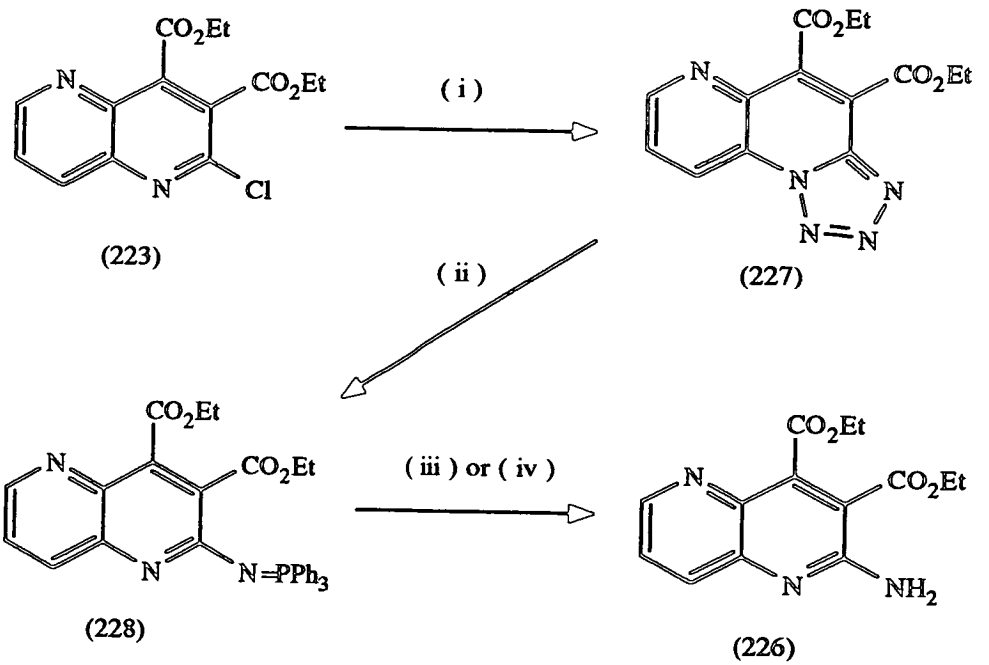
(v) Na, NH_3, -78°.

Scheme 65

2.6 : Studies on the Transformations of Some 1,5-Napthyridine Derivatives

It was deemed of interest to explore the reactivity of some of the new 1,5-napthyridine derivatives whose syntheses were discussed in the previous section and in particular to transform these compounds into products whose functionality would permit their further annulation to afford tricyclic nitrogen heterocycles the interest in which will be discussed in the following section (see Section 2.7).

As mentioned in the previous section (see Section 2.5), 1,5-napthyridines with *ortho*-amino carbonyl functionality are of particular interest as precursors to tricyclic heterocycles. The synthesis of one such compound, ethyl 3-amino-1,5-napthyridin-2-one-4-carboxylate (207), was discussed in the previous section (see Scheme 60). Another interesting target was (Scheme 65) the 2-amino-1,5-napthyridine derivative (226). Diethyl 1,5-napthyridin-2-one-3,4-dicarboxylate (195) was envisaged as the precursor to the amine (226) and in this respect the diester (195) was initially chlorinated in high yield (87%) by treatment with phosphorus oxychloride to give the 2-chloro-1,5-napthyridine derivative (223). However the chloro compound (223) failed to furnish the amine (226) on treatment with liquid ammonia giving only unreacted starting material. The chloro compound (223) did react with the more nucleophilic benzylamine affording the 2-benzylamino derivative (224) in excellent yield (92%). However, attempted debenzylation of the benzylamino compound (224) with sodium in liquid ammonia failed to give the desired amine (226), this reaction resulting in the production of a complex mixture of products. Due to the reluctance of the chlorine substituent in the 1,5-napthyridine (223) to undergo nucleophilic displacement by ammonia, the 2-benzenesulphonyl-1,5-napthyridine (225) was prepared from the chloro compound (223) in the hope that ammonia might more readily displace the benzenesulphonyl group from (225) than the chlorine group from (223). The benzenesulphonyl group has been reported[97] to be an alternative leaving group to a



(i) NaN_3, DMF, 100°.

(ii) PPh_3, dioxane, reflux.

(iii) HCl aqu., dioxane, 50°.

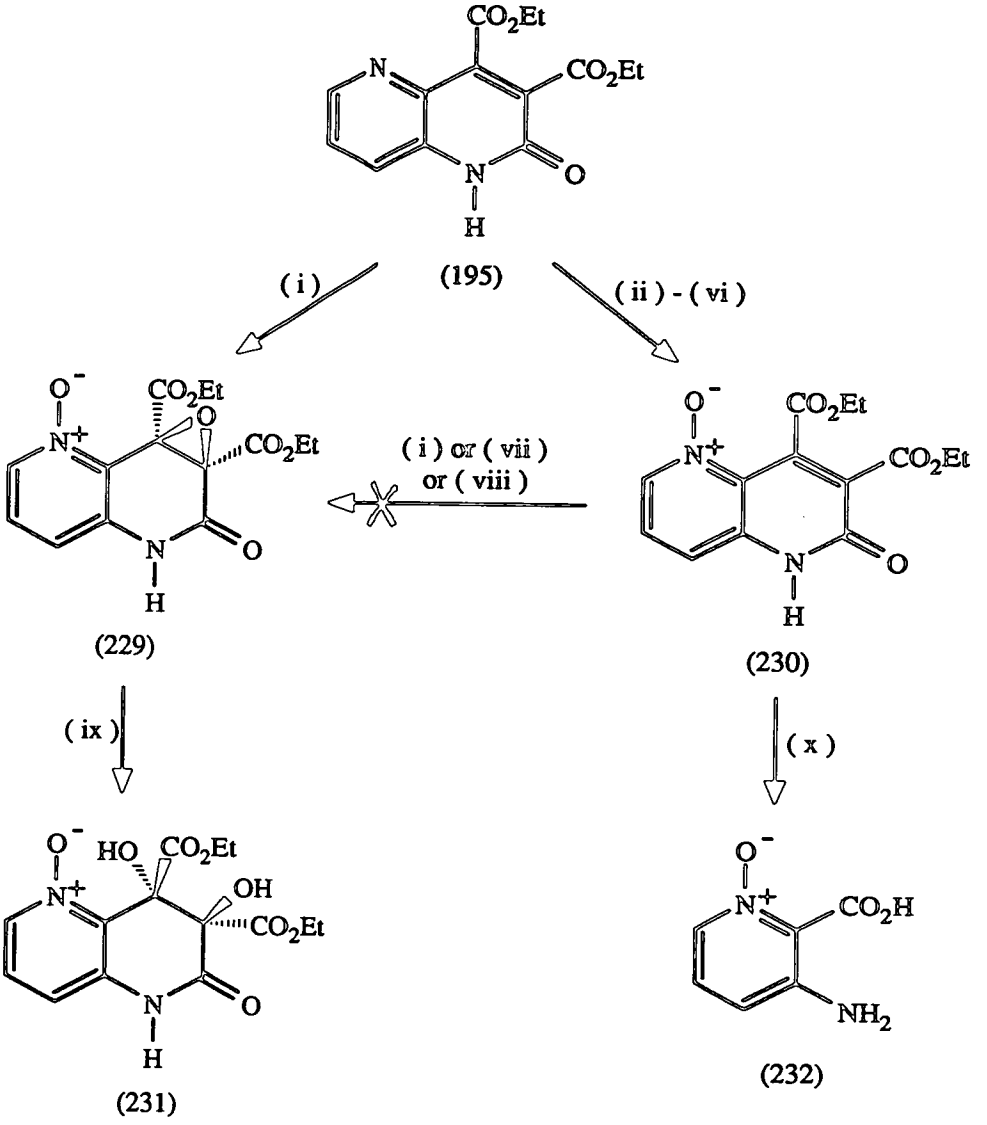
(iv) HCl aqu., dioxane, room temp.

Scheme 66

halogen. However this was found not to be the case, the 2-benzenesulphonyl-1,5-napthyridine (225) being recovered unchanged upon treatment with liquid ammonia.

The synthetic approach to the 2-amino-1,5-napthyridine derivative (226) which ultimately proved to be successful (Scheme 66) started with the reaction of the 2-chloro-1,5-napthyridine (223) with sodium azide to afford an excellent yield of the tetrazolo[1,5-a]-1,5-napthyridine derivative (227). This compound, as expected,[98] showed no evidence in its i.r. spectrum for the alternative azide tautomer. The tetrazole derivative (227) reacted readily with triphenylphosphine to give the phosphinimine (228) which was readily hydrolysed by treatment with aqueous hydrochloric acid at room temperature for 96h or better at 50° for 6h to yield the desired 2-amino-1,5-napthyridine derivative (226). The overall yield for this three step conversion of the 2-chloro-1,5-napthyridine (223) into the 2-amino-1,5-napthyridine (226) proved to be excellent (87%). The use of the 2-amino-1,5-napthyridine (226) for the synthesis of tricyclic heterocycles will be discussed in the following section of this chapter (Section 2.7).

Also investigated (Scheme 67) was the *N*-oxidation of diethyl 1,5-napthyridin-2-one-3,4-dicarboxylate (195) with the eventual aim of in some way inducing further rearrangement of the *N*-oxide product (230) to introduce functionality into the left hand ring (as drawn) of the 1,5-napthyridin-2-one (195). With this aim in mind the diester (195) was treated with peracetic acid to afford after 20h a moderate yield (43%) of a colourless, crystalline solid whose elemental analysis and mass spectrum indicated that two atoms of oxygen have been incorporated into the 1,5-napthyridin-2-one (195). Attempts to reduce this colourless product with sodium dithionite, in an effort to demonstrate the presence of an *N*-oxide substituent by its reconversion into the parent napthyridinone, proved to be unsuccessful. Attempted hydrolysis of the colourless product with aqueous hydrochloric acid gave only unreacted starting material. However, on treatment with aqueous sodium carbonate the colourless product was converted in excellent yield into a pale orange solid whose elemental



(i) 30% H_2O_2 aqu., AcOH, 50°.

(ii) - (vi) see Table 12.

(vii) 90% H_2O_2 aqu., $(CF_3CO)_2O$, CH_2Cl_2, room temp.

(viii) 14% NaOCl aqu., pyridine, room temp.

(ix) 1M Na_2CO_3 aqu., room temp.

(x) 30% H_2O_2 aqu., 1M NaOH aqu., room temp.

Scheme 67

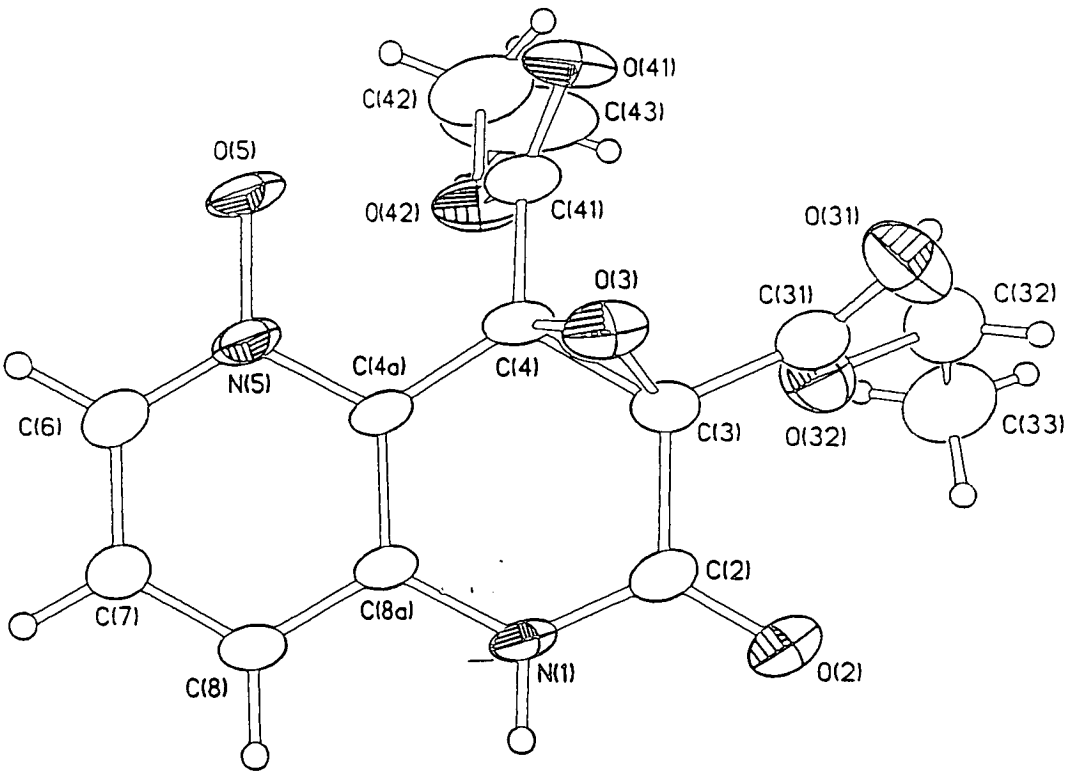
analysis and mass spectrum showed that a molecule of water had been incorporated. Fortunately the identity of the original colourless product was established as the epoxynapthyridinone *N*-oxide (229) by X-ray diffraction analysis of a suitable single crystal (see Figure 3 and Tables 8 and 9). It follows that the pale orange solid obtained by the hydrolysis of the epoxide (229) can be assigned the vicinal diol structure (231). The fact that epoxidation of the 1,5-napthyridin-2-one (195) had occured is surprising due to the electron deficient nature of the C-C double bond in the diester (195) and in an effort to circumvent this unwanted reaction, the 1,5-napthyridin-2-one (195) was subjected to only brief exposure to peracetic acid. However this reaction resulted in only a good recovery of unreacted starting material.

meta-Chloroperbenzoic acid (mCPBA) was next investigated as an alternative reagent to peracetic acid for the *N*-oxidation of (195). Brief exposure of (195) to mCPBA resulted in only a good recovery of the unreacted starting material but by prolonging the reaction time a moderate yield (46%) of the desired *N*-oxide (230) was obtained [see Table 10, entry (ii)], the rest of the material being unreacted

Table 10 ; *N*-Oxidation Reactions of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate (195) with *meta*-Chloroperbenzoic Acid[a]

Entry	No. of Equivalents mCPBA	Reaction Time (h)	Products (% yield)	
			(195)	(230)
(ii)	1.5	2	72	-
(iii)	1.5	17	52	46
(iv)	3	17	17	46
(v)	5	17	7	36
(vi)	3[b]	23	28	59

a, all oxidations were performed in chloroform solution at 50°; b, 1.5 equivalents of mCPBA were added at the start of the reaction followed by a further 1.5 equivalents of mCPBA after 7h.


O(41)
C(42)
C(43)
O(5)
O(42)
C(41)
O(31)
O(3)
C(31)
C(32)
N(5)
C(4a)
C(4)
C(6)
C(3)
O(32)
C(33)
C(2)
C(7)
C(8a)
N(1)
O(2)
C(8)

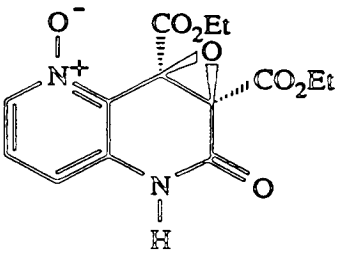

O⁻
N⁺
CO2Et
O
CO2Et
N
H
O

Figure 3

X-Ray Diffraction Data for Diethyl 3,4-Dihydro-3,4epoxy-1,5-napthyridin-2-(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229)

Table 8 : Bond Lengths (Angstroms) with Standard Deviations

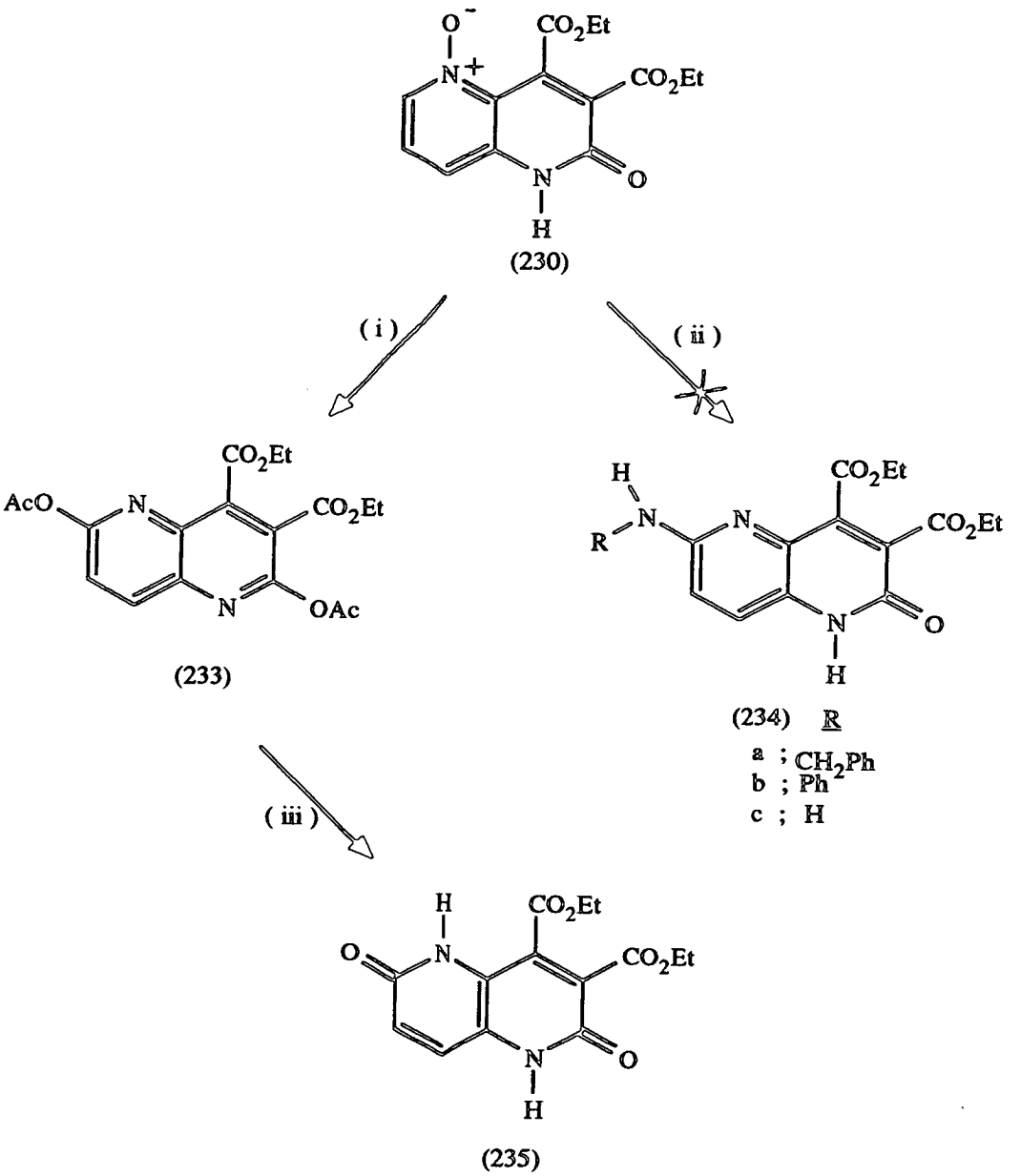
N(1) - C(2)	1.351 (6)	N(1) - C(8A)	1.389 (4)
C(2) - O(2)	1.202 (5)	C(2) - C(3)	1.509 (5)
C(3) - O(3)	1.426 (5)	C(3) - C(4)	1.479 (5)
C(3) - C(31)	1.511 (7)	O(3) - C(4)	1.440 (5)
C(4) - C(4A)	1.464 (5)	C(4) - C(41)	1.513 (5)
C(4A) - N(5)	1.357 (4)	C(4A) - C(8A)	1.388 (4)
N(5) - O(5)	1.316 (3)	N(5) - C(6)	1.336 (6)
C(6) - C(7)	1.373 (5)	C(7) - C(8)	1.365 (6)
C(8) - C(8A)	1.387 (6)	C(31) - O(31)	1.189 (7)
C(31) - O(32)	1.305 (7)	O(32) - C(32)	1.465 (8)
C(32) - C(33)	1.444 (9)	C(41) - O(41)	1.189 (5)
C(41) - O(42)	1.312 (6)	O(42) - C(42)	1.459 (6)
C(42) - C(43)	1.237 (12)		

Table 9 : Bond Angles (Degrees) with Standard Deviations

C(2) - N(1) - C(8A)	125.8 (3)	N(1) - C(2) - O(2)	122.7 (3)
N(1) - C(2) - C(3)	116.5 (3)	O(2) - C(2) - C(3)	120.8 (4)
C(2) - C(3) - O(3)	116.8 (4)	C(2) - C(3) - C(4)	119.7 (3)
O(3) - C(3) - C(4)	59.4 (2)	C(2) - C(3) - C(31)	114.5 (3)
O(3) - C(3) - C(31)	113.8 3()	C(4) - C(3) - C(31)	120.6 (3)
C(3) - O(3) - C(4)	62.1 (2)	C(3) - C(4) - O(3)	58.5 (2)
C(3) - C(4) - C(4A)	116.3 3()	O(3) - C(4) - C(4A)	113.4 (3)
C(3) - C(4) - C(41)	117.5 (3)	O(3) - C(4) - C(41)	115.8 (3)
C(4A) - C(4) - C(41)	120.1 (3)	C(4) - C(4A) - N(5)	118.7 (3)
C(4) - C(4A) - C(8A)	121.5 (3)	N(5) - C(4A) - C(8A)	119.5 (3)
C(4A) - N(5) - O(5)	118.0 (3)	C(4A) - N(5) - C(6)	121.5 (3)
O(5) - N(5) - C(6)	120.6 (3)	N(5) - C(6) - C(7)	119.6 (4)
C(6) - C(7) - C(8)	121.2 (4)	C(7) - C(8) - C(8A)	118.5 (3)
N(1) - C(8A) - C(4A)	119.9 (3)	N(1) - C(8A) - C(8)	120.6 (3)
C(4A) - C(8A) - C(8)	119.5 (3)	C(3) - C(31) - O(31)	124.7 (5)
C(3) - C(31) - O(32)	108.6 (4)	O(31) - C(31) - O(32)	126.6 (5)
C(31) - O(32) - C(32)	116.7 (4)	O(32) - C(32) - C(33)	108.3 (5)
C(4) - C(41) - O(41)	124.8 (4)	C(4) - C(41) - O(42)	108.5 (3)
O(41) - C(41) - O(42)	126.6 (4)	O(41) - O(42) - C(42)	116.2 (4)
O(42) - C(42) - C(43)	115.4 (5)		

napthyridinone (195). The results obtained from experiments carried out to optimise the yield of the *N*-oxide (230) in the mCPBA oxidation of the napthyridinone (195) are presented in Table 10. It can be seen that increasing the number of equivalents of mCPBA gave little or no improvement in the yield of the *N*-oxide (230) [entries (iii) - (v)]. The optimum conditions established involved the use of three equivalents of mCPBA added in two portions [entry (vi)] and this resulted in the formation of the *N*-oxide (230) in 59% yield. A final attempt to oxidise the napthyridinone (195) using the alternative reagent, potassium peroxymonosulphate (OXONE™)[99] resulted only in a good recovery of unreacted starting material. An attempt to reduce the *N*-oxide (230) back to the parent 1,5-napthyridin-2-one (195) with sodium dithionite proved to be unsuccessful giving only a complex mixture of products.

Due to the surprising isolation of the epoxynapthyridinone (229) by the peracetic acid oxidation of the napthyridinone (195) it was of relevance to acertain whether the *N*-oxide (230) could be epoxidised to give the epoxynapthyridine *N*-oxide (229). However, this transformation [(230) → (229)] could not be brought about by either peracetic acid, the stronger reagent trifluoroperacetic acid or by sodium hypochlorite, a reagent which is known to epoxidise electron-deficient C-C double bonds.[100] With the first two reagents only unreacted starting material was obtained while with hypochlorite only a complex mixture of products was formed. In a further attempt to effect its epoxidation the 1,5-napthyridin-2-one *N*-oxide (230) was treated with alkaline hydrogen peroxide. However this reagent resulted in the degradation of the starting material to afford a grey solid which is formulated as 3-aminopicolinic acid *N*-oxide (232) on the basis of its spectroscopic data. Unfortunately insufficient material was available to rigorously characterise (232) by elemental analysis and the exact mode of formation of the picolinic acid (232) from the napthyridinone (230) remains unclear at present. The failure of the *N*-oxide (230) to epoxidise while the free napthyridine (195) does react in this manner to afford the epoxide (229) may be due to the fact that in the former compound the adjacency of the positively charged nitrogen atom is



(i) Ac_2O, reflux.
(ii) RN=C=O, dioxane, reflux.
(iii) EtOH, H_2O, reflux.

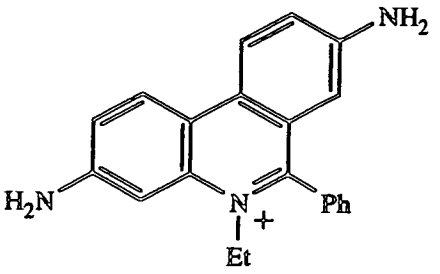
Scheme 68

causing the C-C double bond to become too electron deficient to react with the oxidising agents which were employed. However these results do indicate that during the transformation [(195) → (229)] the epoxidation step preceeds the *N*-oxidation step.

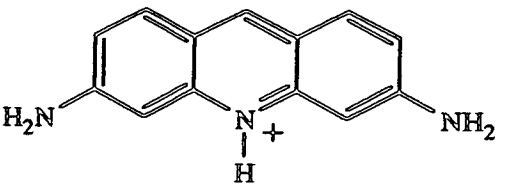
With the 1,5-napthyridin-2-one *N*-oxide (230) now in hand it was next decided to investigate its rearrangement reactions (Scheme 68).[101,102] On heating a solution of the *N*-oxide (230) in acetic anhydride under reflux a 41% yield of the diacetoxy derivative (233) was obtained, the initially expected monoacetoxy rearrangement product obviously undergoing subsequent O-acetylation of the lactam functionality. Also produced was a low yield (22%) of the 1,5-napthyridine-2,6-dione (235) which presumably arises from the in situ hydrolysis of the diacetoxy derivative (233). The 1,5-napthyridine-2,6-dione (235) could also be prepared from the *N*-oxide (230) in 69% yield by the hydrolysis with refluxing aqueous ethanol of the crude product from the acetic anhydride rearrangement of the *N*-oxide (230) without isolation of the intermediate diacetoxy derivative (233).

The 1,5-napthyridin-2-one *N*-oxide (230) was also treated with benzyl isocyanate in refluxing dioxane solution in the hope that the 6-benzylamino-1,5-napthyrid-2-one derivative (234a) would be obtained[103] and that this product could then be debenzylated to afford the 6-amino-1,5-napthyridin-2-one derivative (234c). However, this reaction gave only a good recovery of unreacted starting material (230) as did an analogous attempt to prepare the 6-phenylamino-1,5-napthyridin-2-one derivative (234b) by the reaction of the *N*-oxide (230) with phenyl isocyanate in refluxing dioxane solution.

Due to time limitations and the limited availability of the 1,5-napthyridin-2-one *N*-oxide (230), further investigations on the rearrangement reactions of the *N*-oxide (230) were not undertaken.

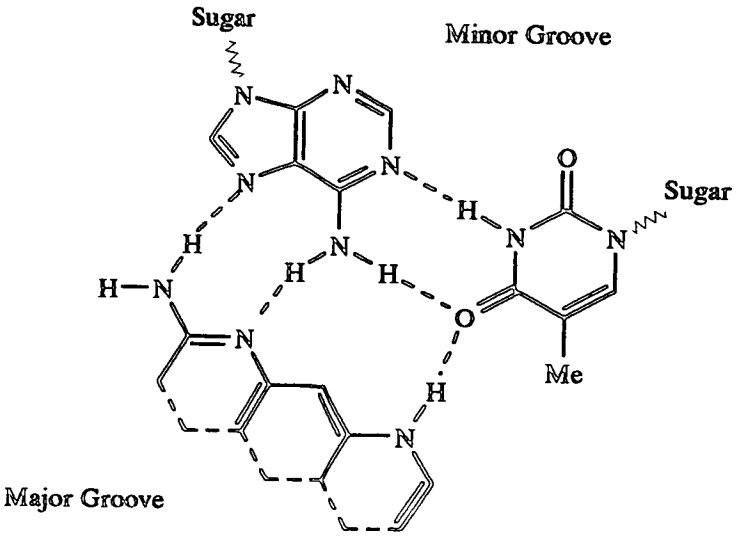


(236)



(237)

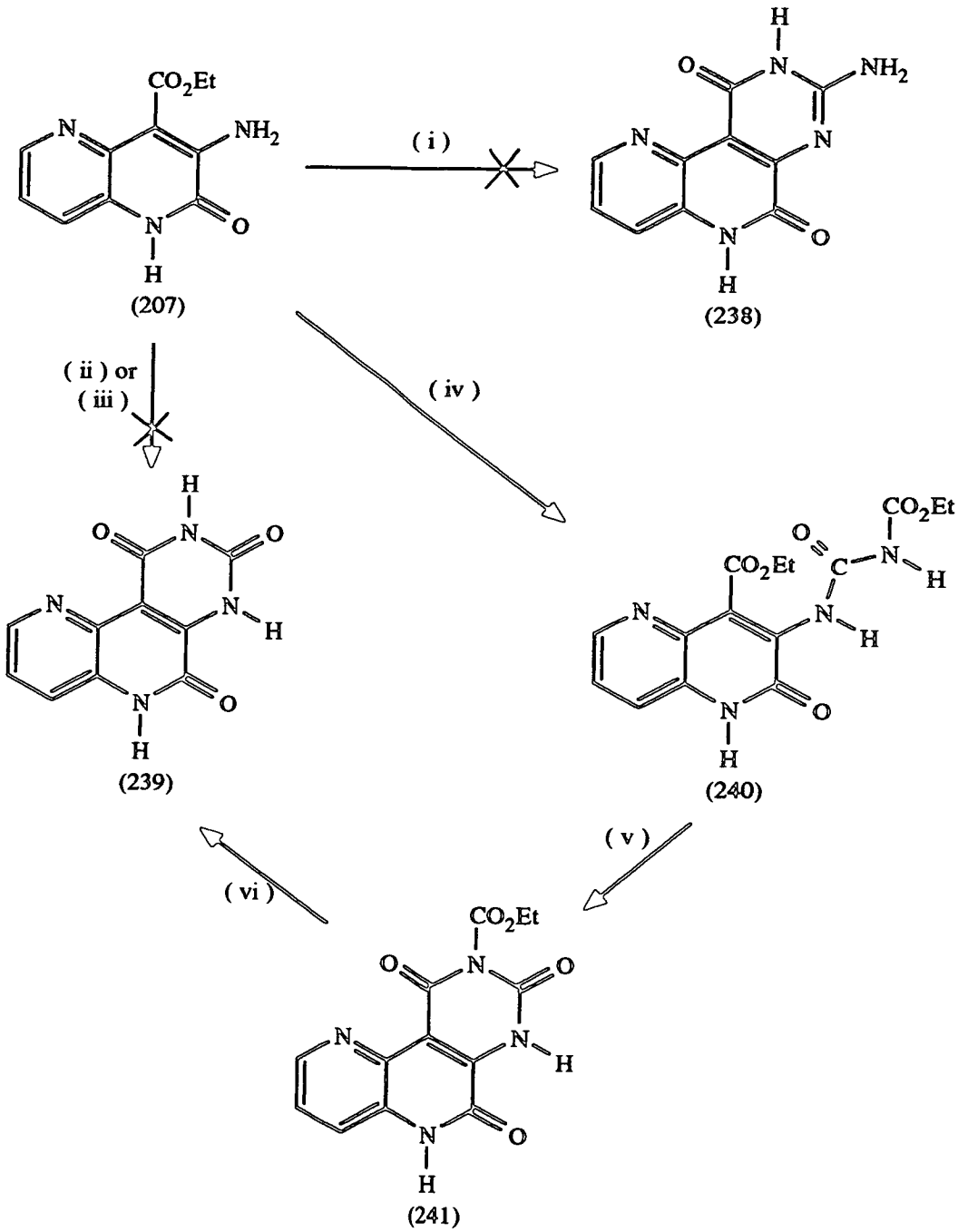
Scheme 69



Scheme 70

2.7 : Studies on the Synthesis of Some Pyrimidonapthyridine Derivatives

As was mentioned in the previous two sections of this chapter (see Sections 2.5 and 2.6) it was of interest to elaborate the functionalised napthyridines which were prepared during the present investigations into tricyclic heterocycles. Of particular interest is the fusion of a further pyrimidine ring onto the napthyridine nucleus. The reasons for this aim are that the tricyclic molecules so prepared might have the capacity to bind to DNA. This can be envisaged to occur by either of two possible mechanisms. These planar tricyclic molecules may have the capacity to intercalate[104] between the base pairs of DNA in a manner similar to other well known[105] intercalating agents (Scheme 69) such as ethidium (236) and proflavine (237). Alternatively such tricyclic molecules may have the capacity to patricipate in site-specific hydrogen-bonding in the major groove of DNA in a fashion analogous to the well known[104] triple-helix formation that can occur with certain sequences of DNA. Scheme 70 shows an example of a generalised tricyclic heterocyclic structure which is envisaged to form specific hydrogen-bonding interactions to an adenine-thymine base pair in the major groove of duplex DNA. Triple helical structures are known[106] to occur *in vivo* and are implicated in a number of biological proceses.[104,106] Therefore a chemotherapeutic strategy based on site-specific interaction with DNA by small molecules may be possible. The precise spatial arrangement of the hydrogen bonding sites in the small molecules is crucial for such interactions to occur. Altering the molecular framework of such binding agents will dramatically affect their ability to form hydrogen bonds. Therefore it is possible that in the future individual DNA base pairs might be specifically bound by small molecules such as the tricyclic heterocycles discussed here. Taking this approach further still, it might become possible, by the joining together of a number of these heterocycles in a predetermined order, to bind to specific sequences of DNA. The effect of this binding might be to alter or prevent the



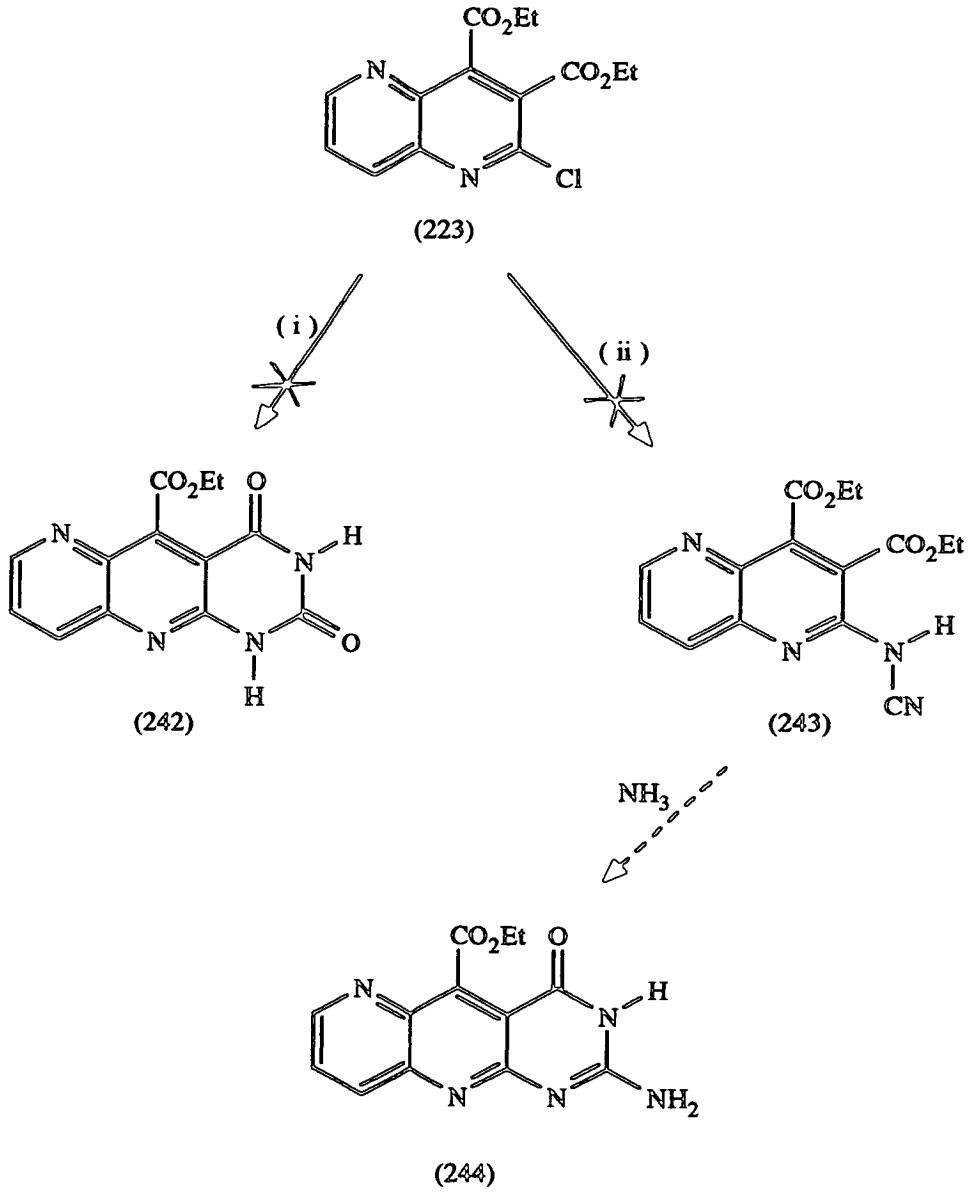
(i) H_2NCN, xylene, reflux.
(ii) KCNO, HCl, water, room temp.
(iii) H_2NCO_2Et, xylene, reflux.
(iv) $EtO_2CN{=}C{=}O$, DMF, room temp.
(v) 2M NaOH aqu., room temp.
(vi) 2M NaOH aqu., reflux.

Scheme 71

expression of these sequences of DNA hopefully to the ultimate benefit of the host organism.

There are many methods available for the construction of fused pyrimidines from aromatic or heteroaromatic substrates containing *ortho*-aminocarbonyl functionality.[69,107] To begin with (Scheme 71) the 3-amino-1,5-napthyridin-2-one-4-carboxylate (207) was chosen as a suitable precursor of the desired pyrimidonapthyridines. Applying a standard synthetic method for the synthesis of quinazolines,[107] the reaction of the 3-aminonapthyridine derivative (207) with potassium cyanate was attempted. It was hoped that this reaction would afford the fused pyrimidine-2,4-dione derivative (239) but it resulted only in the recovery of unreacted starting material .A further attempt to obtain the fused pyrimidinedione (239) via the thermal condensation of the 3-aminonapthyridine derivative (207) with ethyl carbamate also was also unsuccessful, again giving only unreacted starting material. In another standard synthetic method,[107] this time for the construction of fused 2-aminopyrimidin-4-ones, an attempt was made to condense the 3-aminonapthyridine (207) with cyanamide. It was anticipated that this would afford the tricyclic derivative (238) but unfortunately gave only unreacted starting material.

In the light of these failures it was next decided to adopt a different approach to the synthesis of the tricyclic derivative (239) via condensation of the 3-aminonapthyridine derivative (207) with a suitable isocyanate followed by cyclisation of the urea so produced to give the tricycle. The synthesis of fused pyrimidines by this approach is well known[108,109] and so in the present studies the 3-aminonapthyridine derivative (207) was treated with ethoxycarbonyl isocyanate, itself prepared by a literature procedure.[110] This reaction afforded the anticipated disubstituted urea derivative (240) in excellent yield (93%). On treatment with aqueous sodium hydroxide at room temperature the urea (240) underwent cyclisation to afford a good yield of the *N*-ethoxycarbonyl pyrimidonapthyridinetrione derivative (241). Removal of the ethoxycarbonyl group from (241) was achieved by heating a suspension of the



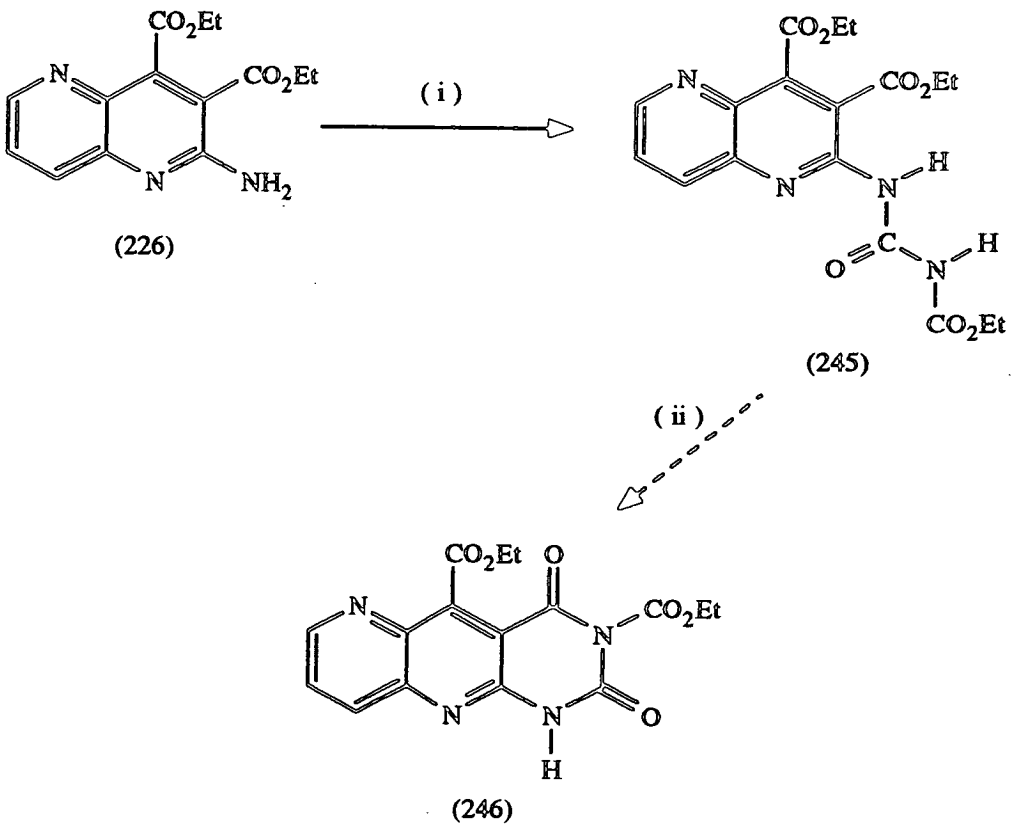
(i) H_2NCONH_2, DMF, reflux.

(ii) NaNHCN, DMF, 100°.

Scheme 72

tricycle (241) in aqueous sodium hydroxide under reflux. These conditions resulted in hydrolysis and decarboxylation to give a quantitative yield of the desired pyrimido[4,5-c]-1,5-napthyridine-2,4,6-trione (239). The i.r., ^1H n.m.r. and mass spectroscopic data for the tricycle (239) were all in agreement with the assigned structure. However due to the highly insoluble nature of this solid compound it could not be purified by crystallisation and therefore no satisfactory elemental analysis could be obtained.

With the angularly fused tricyclic derivative (239) in hand attention was next turned to the synthesis of analogous linearly fused tricyclic heterocycles. Initially (Scheme 72) the utility of the 2-chloro-1,5-napthyridine derivative (233) was investigated in this respect. However in preliminary experiments the chloro compound (233) failed to react with urea to give the expected product, the tricycle (242). Also 2-chloro-1,5-napthyridine (233) failed to condense with sodium cyanamide to give the cyanamide derivative (243) from which it was hoped to eventually obtain the tricyclic derivative (244). This approach was therefore abandoned and annulation (Scheme 73) of the 2-aminonapthyridine derivative (226) was studied instead. To this end, the amine (226) was treated with ethoxycarbonyl isocyanate in DMF at room temperature and this reaction did indeed afford the desired urea derivative (245) however in only 20% yield, along with unreacted starting material (226) (51%). The urea (245) crystallised very well from ethanol to give large colourless crystals of a suitable quality for X-ray diffraction analysis (see Figure 4 and Tables 11 and 12) which conclusively established its structure. In an attempt to improve the yield of the urea (245), the reaction of the amine (226) with ethoxycarbonyl isocyanate was performed in refluxing DME solution but these conditions gave only a 14% yield of the desired urea product (245). However it was gratifying to find that by heating a solution of the amine (226) in DME under reflux with an excess (three equivalents) of ethoxycarbonyl isocyanate a near quantitative yield of the urea (245) was obtained. The behaviour of this urea (245) towards hydrolysis by aqueous sodium hydroxide was next investigated. Stirring at room temperature for 0.5h in aqueous alkali did indeed afford a colourless solid



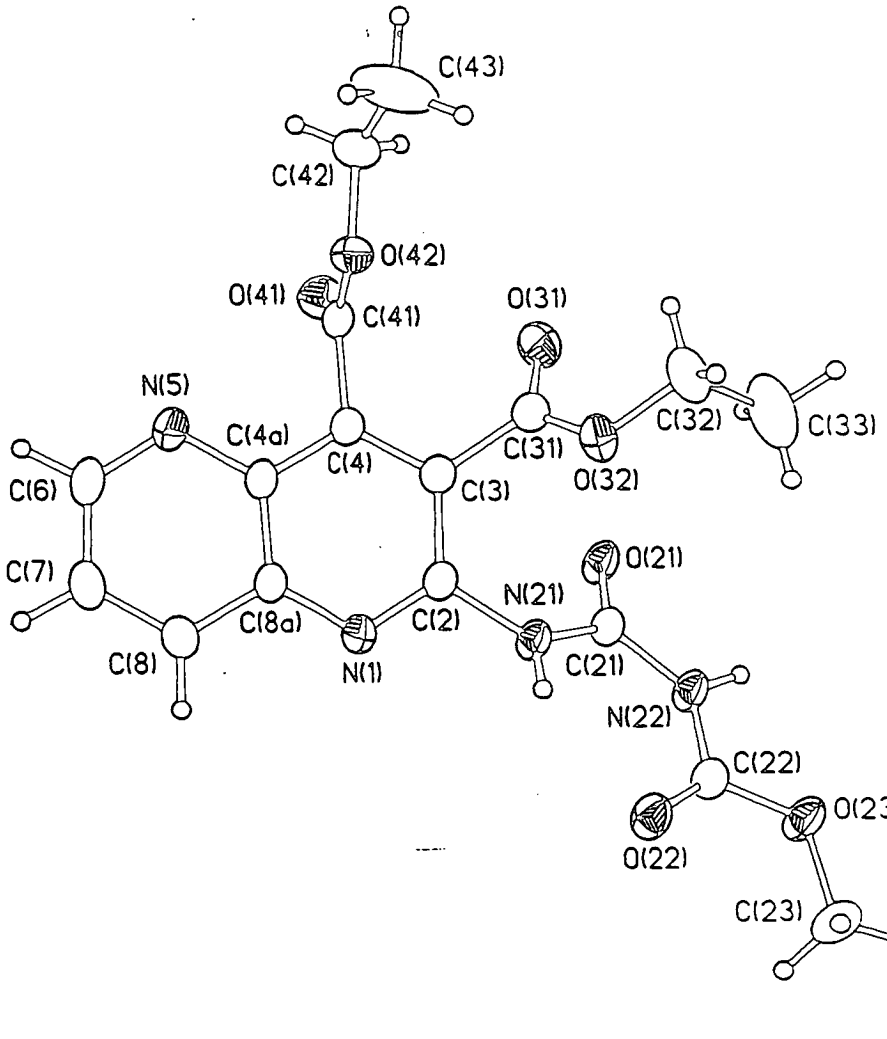
(i) $EtO_2CN{=}C{=}O$, DME, reflux.

(ii) 2M NaOH aqu., room temp.

Scheme 73

product in moderate yield which is tentatively formulated as a hydrate of the anticipated *N*-ethoxycarbonyl pyrimidonapthyridine (246). The ^1H n.m.r. spectrum of the product shows the presence of two ethyl ester groups, three aromatic protons and two D_2O exchangeable protons while its i.r. spectrum exhibits four discernable carbonyl stretching frequences at 1784, 1734, 1697 and 1670 cm^{-1} all of which data is in agreement with the assigned structure (246). In particular, the carbonyl stretching frequency at 1784 cm^{-1} suggests the presence of an *N*-ethoxycarbonyl functionality, since the analogous *N*-ethoxycarbonyl derivative (241) (Scheme 71) shows a similar absorbtion at 1780 cm^{-1}. However, no appropriate molecular ion for the tricycle (246) was observed in either its electron impact or fast atom bombardment mass spectra and its elemental analysis was outwith acceptable error limits. The assignment of structure (246) to the product derived from treatment of the urea (245) with aqueous sodium hydroxide must therefore still remain tentative.

Unfortunately due to time limitations and the limited availability of adequate amounts of materials, further investigations on the cyclisation of the urea (245) and the firm identification of the proposed tricyclic product (246) have not been undertaken at present.


C(43)
C(42)
O(42)
O(41)
C(41)
O(31)
N(5)
C(4a)
C(4)
C(31)
C(32)
C(33)
C(6)
C(3)
O(32)
C(7)
O(21)
N(21)
C(8a)
C(2)
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N(1)
C(21)
N(22)
C(22)
O(23)
O(22)
C(23)
C(24)

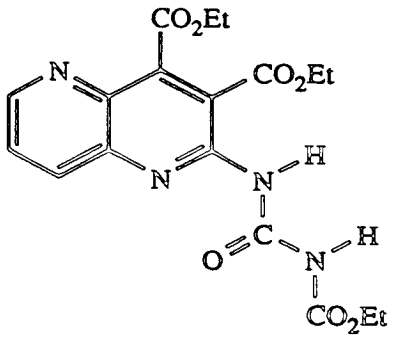

CO2Et
CO2Et
N
N
N
H
O
C
N
H
CO2Et

Figure 4

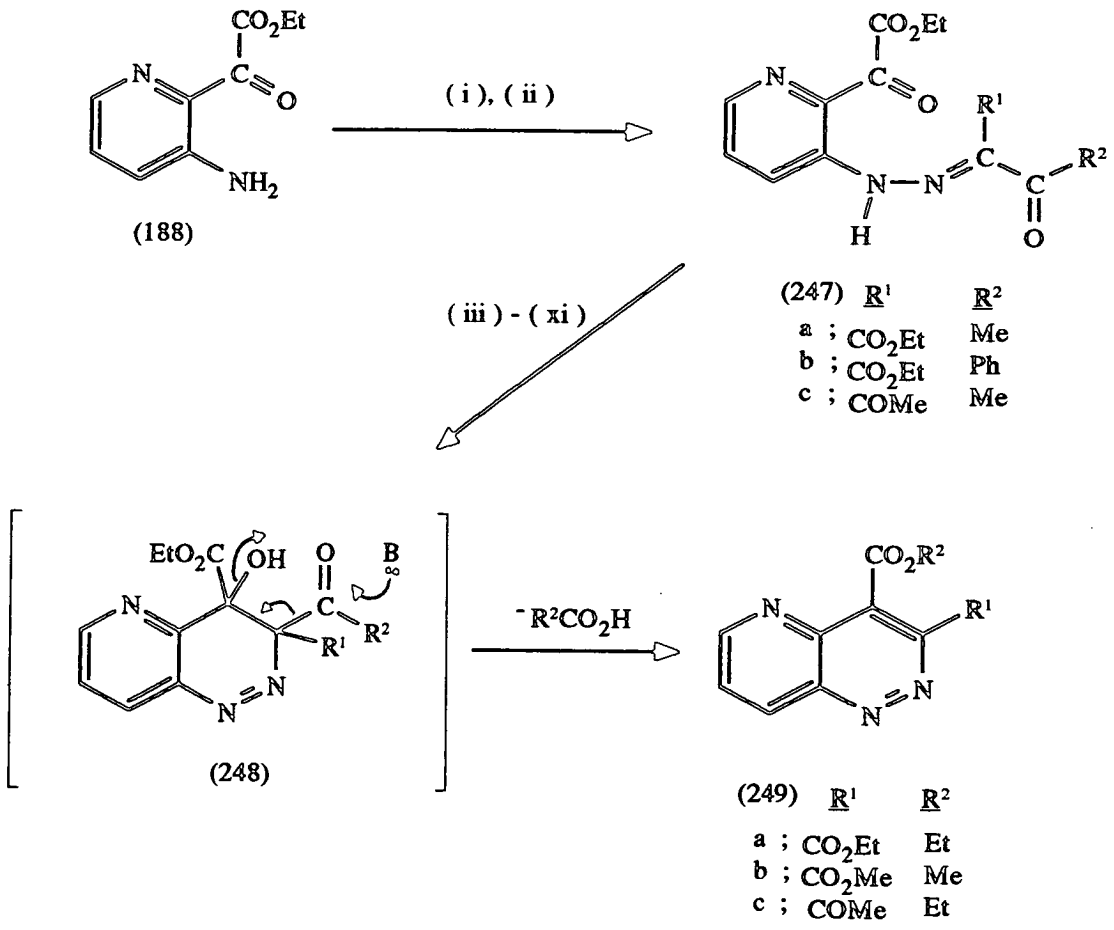
X-Ray Diffraction Data for 1-(3,4-Diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245)

Table 11 : Bond Lengths (Angstroms) with Standard Deviations

N(1) - C(2)	1.298 (3)	N(1) - C(8A)	1.381 (3)
C(2) - C(3)	1.442 (3)	C(2) - N(21)	1.424 (3)
C(3) - C(4)	1.384 (4)	C(3) - C(31)	1.476 (3)
C(4) - C(4A)	1.405 (3)	C(4) - C(41)	1.530 (4)
C(4A) - N(5)	1.381 (3)	C(4A) - C(8A)	1.420 (3)
N(5) - C(6)	1.306 (3)	C(6) - C(7)	1.403 (4)
C(7) - C(8)	1.374 (4)	C(8) - C(8A)	1.393 (3)
N(21) - C(21)	1.354 (3)	C(21) - O(21)	1.239 (3)
C(21) - N(22)	1.400 (3)	N(22) - C(22)	1.387 (3)
C(22) - O(22)	1.200 (3)	C(22) - O(23)	1.337 (3)
O(23) - C(23)	1.475 (4)	C(23) - C(24)	1.459 (5)
C(31) - O(31)	1.207 (3)	C(31) - O(32)	1.349 (4)
O(32) - C(32)	1.424 (4)	C(32) - C(33)	1.446 (6)
C(41) - O(41)	1.200 (4)	C(41) - O(42)	1.307 (4)
O(42) - C(42)	1.457 (3)	C(42) - C(43)	1.414 (6)

Table 12 : Bond Angles (Degrees) with Standard Deviations

C(2) - N(1) - C(8A)	117.4 (2)	N(1) - C(2) - C(3)	123.0 (2)
N(1) - C(2) - N(21)	113.4 (2)	C(3) - C(2) - N(21)	123.5 (2)
C(2) - C(3) - C(4)	119.4 (2)	C(2) - C(3) - C(31)	123.1 (2)
C(4) - C(3) - C(31)	117.2 (2)	C(3) - C(4) - C(4A)	118.8 (2)
C(3) - C(4) - C(41)	123.7 (2)	C(4A) - C(4) - C(41)	117.5 (2)
C(4) - C(4A) - N(5)	118.4 (2)	C(4) - C(4A) - C(8A)	117.1 (2)
N(5) - C(4A) - C(8A)	124.4 (2)	C(4A) - N(5) - C(6)	115.4 (2)
N(5) - C(6) - C(7)	124.2 (3)	C(6) - C(7) - C(8)	120.7 (2)
C(7) - C(8) - C(8A)	118.0 (2)	N(1) - C(8A) - C(4A)	123.9 (2)
N(1) - C(8A) - C(8)	118.8 (2)	C(4A) - C(8A) - C(8)	117.2 (2)
C(2) - N(21) - C(21)	122.0 (2)	N(21) - C(21) - O(21)	122.6 (2)
N(21) - C(21) - N(22)	117.4 (2)	O(21) - C(21) - N(22)	120.0 (2)
C(21) - N(22) - C(22)	129.1 (2)	N(22) - C(22) - O(22)	124.9 (2)
N(22) - C(22) - O(23)	110.2 (2)	O(22) - C(22) - O(23)	124.8 (2)
C(22) - O(23) - C(23)	117.9 (2)	O(23) - C(23) - C(24)	110.2 (2)
C(3) - C(31) - O(31)	123.2 (3)	C(3) - C(31) - O(32)	109.9 (2)
O(31) - C(31) - O(32)	126.7 (2)	C(31) - O(32) - C(32)	116.3 (2)
O(32) - C(32) - C(33)	112.4 (3)	C(4) - C(41) - O(41)	125.0 (3)
C(4) - C(41) - O(42)	109.7 (2)	O(41) - C(41) - O(42)	125.3 (2)
C(41) - O(420 - C(42)	116.1 (2)	O(42) - C(42) - C(43)	107.2 (3)



(i) $NaNO_2$, HNO_3, water, 0-5°.

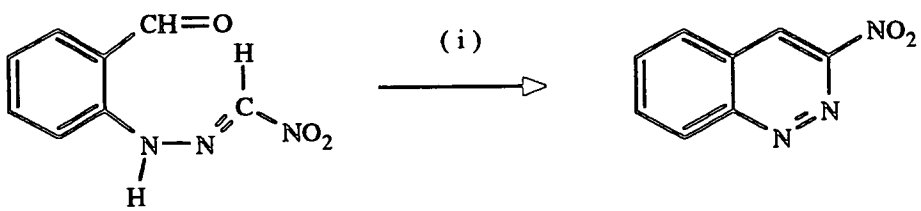
(ii) $R^1CH_2COR^2$, NaOAc, H_2O, EtOH, room temp.

(iii) - (xi) see Table 13.

Scheme 74

2.8 : Studies on the Synthesis of Some Pyrido[3,2-c]pyridazine Derivatives

As a further extension (Scheme 74) of the synthetic utility of the aminopyridyl ketone (188), its conversion into the functionalised pyridopyridazine derivatives (249) was investigated. It was initially speculated that the hydrazone intermediates (247) required for this heterocyclic synthesis would be readily available through diazotisation of the amine (188) and subsequent coupling of the resulting diazonium species with carbonyl compounds containing an α-methylene group such as $\beta-$ketoesters and $\beta-$diketones.[111] It was then believed that treatment of these hydrazones (247) with base would promote cyclisation to the bicyclic intermediates (248) from which an acyl group can be cleaved by the base to finally afford the desired pyrido[3,2-c]pyridazine derivatives (249). This latter cleavage reaction is involved in the Japp-Klingemann synthesis of hydrazones.[112] The base-catalysed cyclisation of 2-acyl arylhydrazones to afford fused cinnolines has been the subject of only a few reports[113,114,115] typified (Scheme 75) by the synthesis of 3-nitrocinnoline (251) by the cyclisation of the hydrazone derivative (250).[113] However no such analogous cyclisation of 2-acyl heteroaromatic hydrazones has been reported to date although it should be noted that pyrido[3,2-c]pyridazines have been synthesised using a number of different methodologies.[116]



(250) (251)

(i) NaOH aqu., room temp.

Scheme 75

Table 13 : Base-catalysed Cyclisation Reactions of N-(2-Ethoxalylpyrid-3-yl) hydrazones (247a-c)

Entry	Substrate	Base[a]	Solvent	Reaction Temp (°C)	Product	% Yield
(iii)	(247a)	NaOEt	EtOH	78	b	-
(iv)	(247a)	piperidine	EtOH	78	(249a)	27
(v)	(247a)	piperidine	EtOH	20	b	-
(vi)	(247a)	Et_3N	EtOH	78	(249a)	40
(vii)	(247a)	Et_3N[c]	EtOH	78	(249a)	22
(viii)	(247a)	$PhCH_2N^+Et_3OH^-$	MeOH	20	(249b)	43
(ix)	(247b)	Et_3N	EtOH	78	(249a)[d]	12
(x)	(247c)	Et_3N	EtOH	78	(249c)	33

a, except where noted one equivalent of the appropriate base was used ; b, no identifiable material was obtained; c, two equivalents of triethylamine were used; d, also isolated was some unreacted starting material [(258a); 63%].

In practice it was pleasing to find that on diazotisation of the aminopyridyl ketone (188) and then coupling with ethyl acetoacetate in the presence of sodium acetate a good yield (66%) of the desired hydrazone (247a) was obtained. The results obtained in the investigations of the base-catalysed cyclisation reactions of the hydrazone (247a) are presented in Table 13. Exposure of (247a) to sodium ethoxide in refluxing ethanol [entry (iii)] gave an intense red solution indicating that the anion of the hydrazone was being formed[113] but unfortunately no identifiable products could be obtained under these reaction conditions. However it was gratifying to find that on heating an ethanolic solution of the hydrazone (247a) under reflux in the presence of one equivalent of piperidine [entry (iv)] the desired pyrido[3,2-c]pyridazine (249a) derivative was indeed formed, albeit in only 27% yield. An attempt to improve this yield by carrying out the piperidine-catalysed cyclisation of (247a) at room temperature [entry (v)] was unsuccessful giving no identifiable material. A slight improvement in the yield of the pyrido[3,2-c]pyridazine (249a) (40%) was achieved by catalysing the cyclisation of the hydrazone (247a) with triethylamine [entry (vi)] and it is of interest to note that by increasing the amount of triethylamine [entry (vii)] a lower yield (22%) of the desired pyrido[3,2-c]pyridazine (249a) was obtained. By using a methanolic solution of the commercially available benzyl triethylammonium hydroxide (Triton B™) as the base for the cyclisation of the hydrazone (247a), a moderate yield (43%) of dimethyl pyrido[3,2-c]pyridazine-3,4-dicarboxylate (249b) was obtained wherein ester exchange from ethyl to methyl has occurred [entry (viii)]. Since these various cyclisation reactions of the hydrazone (247a) were at best giving only low yields of cyclised products (249a) or (249b), the cyclisation of the structurally related hydrazone (247b) was next investigated. It was hoped that the benzoyl group in the hydrazone (247b) would be more readily cleaved off than the acetyl group in the analogous hydrazone (247a) thus resulting in an improved yield of the pyridopyridazine derivative (249a). In practice the hydrazone (247b) was readily prepared by diazotisation of the amine (188) followed by coupling with ethyl

benzoylacetate. However the triethylamine-catalysed cyclisation of the hydrazone (247b) [entry (ix)] afforded only a low yield (12%) of the desired cyclic product (249a) along with 63% of unreacted starting material (247b).

The aminopyridyl ketone (188) was also diazotised and coupled with acetylacetone to afford a good yield of the hydrazone (247c). However the efficienct of the triethylamine-catalysed cyclisation of this hydrazone (247c) also proved to be disappointing [entry (x)] giving only a low yield (39%) of the desired pyrido[3,2-c]pyridazine derivative (249c).

Due to the low yields of cyclised products obtained, further investigations on the base-catalysed cyclisation reactions of the hydrazone derivatives (247) were therefore not undertaken during the present studies.

2.9 : Experimental

General Experimental Details

Infrared spectra were recorded using Perkin-Elmer 298 or Bio-Rad FTS-7 spectrophotometers and bands were strong and sharp unless specified as br (broad) or w (weak). Solids were measured as suspensions (mulls) in Nujol and liquids as thin films.

^{1}H n.m.r. spectra were measured in the stated solvent at 80 MHz using a Bruker WP-80SY instrument, at 200 MHz using a Bruker 200SY instrument, or at 360 MHz using a Bruker WH-360 instrument. Signals were sharp unless specified as b (broad); s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet and m = multiplet. ^{13}C n.m.r. spectra were measured in the stated solvent at 50 MHz using a Bruker 200SY spectrometer and were fully decoupled. Signals were sharp and quat = quaternary carbon atom. Quaternary carbon atoms and methylene groups were identified by $3\pi/4$ DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence spectra.

Electron Impact (EI) mass spectra were recorded at 70 eV on A.I.E. MS-902 and Kratos MS-50TC instruments. Fast Atom Bombardment (FAB) mass spectra were recorded on a Kratos MS-50TC instrument for matrices in thioglycerol.

X-ray diffraction data were collected using a Stoe-Stadi four circle diffractometer on single crystals grown from the stated crystallisation solvent.

Elemental analyses were determined using Carlo-Erba Strumentazione 1106 or Perkin-Elmer 2400 elemental analysers. Routine melting points (m.p.) were caried out using a Gallenkamp apparatus and are uncorrected. Melting points of analytical samples were determined using a Kofler hot-stage apparatus and are uncorrected.

Unless specified, all reagents were laboratory grade. Sodium hydride was a 60% or 80% suspension in mineral oil and was washed with anhydrous diethyl ether before use. Anhydrous triethylamine and ethyldiisopropylamine were prepared by

distillation from calcium hydride and then were stored over anhydrous 4A molecular sieves until used.

Solvent were of technical grade unless otherwise stated. Hexane was distilled prior to use in flash-chromatography. Anhydrous solvents were prepared as follows: xylene was distilled and stored over sodium wire; diethyl ether, benzene and toluene were stored over sodium wire; methylene chloride, chloroform, dimethylformamide, methanol, mesitylene and acetonitrile were distilled and stored over anhydrous 4A molecular sieves; diglyme, 1,2-dimethoxyethane, 1,4-dioxane and pyridine were distilled from calcium hydride and stored over anhydrous 4A molecular sieves; ethanol was distilled from magnesium and stored over anhydrous 4A molecular sieves.

Organic extracts were dried over anhydrous magnesium sulphate prior to filtration and distillation under reduced pressure. Atmospheric moisture was excluded from reaction mixtures using a guard-tube containing self-indicating silica gel (Fisons 6-16 mesh).

Wet column flash-chromatography was carried out over silica (Fluka Kieselgel 60, 220-440 mesh) or alumina (Merck Aluminoxid 90, 70-230 mesh). Dry column flash-chromatography was carried out over silica (Fluka Kieselgel GF_{254}). Thin layer chromatography (t.l.c) was carried out using Polygram Sil' G/UV_{254} or ALOXN/ UV_{254} precoated plastic sheets.

Elemental Analyses and Mass Spectroscopic Data.

Elemental analyses and mass spectroscopic data are collected in Table 14, pages 217-222.

Ethyl 2-Benzenesulphonylethanoate

A solution of sodium benzenesulphinate (16.4g; 0.1mol) in anhydrous dimethylformamide (50.0ml) was treated dropwise with a solution of ethyl 2-bromoethanoate (16.7g; 0.1mol) in anhydrous dimethylformamide (50.0ml) and the

resulting solution was stirred and heated at 120° (oil-bath) with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated and the residue was treated with water (100ml) to give a suspension which was filtered to afford ethyl 2-benzenesulphonylethanoate (17.7g; 78%) as a colourless solid, m.p. 40-42° (lit.[117] 40-41°).

2-(3-Nitropyrid-2-yl)ethanoates (102a-d), (105a), (105b), (105d), (105e) and (118)

A stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of the appropriate ethanoate derivative (0.11mol) in anhydrous dimethylformamide (25.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min, then treated with a solution of 2-chloro-3-nitropyridine (101) (7.9g; 0.05mol) in anhydrous dimethylformamide (25.0ml). The resulting red solution was stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) Diethyl 2-(3-Nitropyrid-2-yl)propanedioate (102a)

The mixture from diethyl propanedioate was diluted with water (25.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (75.0ml). The resulting solution was acidified with concentrated hydrochloric acid and the precipitated solid collected to afford diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (89%) which formed colourless, irregular crystals, m.p. 62-63° (from hexane-diethyl ether) (lit.[118] 63-64°) ν_{max} 1750 and 1730 (C=O) and 1530 and 1350 (NO_2) cm $^{-1}$, δ_H ($CDCl_3$) 8.80 (1H, dd, J = 5 and 2 Hz, ArH), 8.46 (1H, dd, J = 8 and 2 Hz, ArH), 7.49 (1H, dd, J = 8 and 5

Hz, ArH), 5.51 (1H, s, CH), 4.29 (4H, q, J = 7 Hz, 2 x CH_2) and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

Extraction of the aqueous mother liqour with methylene chloride gave a red oil whose t.l.c in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture containing mainly unreacted diethyl propanedioate, which therefore was not further investigated.

(ii) Dimethyl 2-(3-Nitropyrid-2-yl)propanedioate (102b)

The mixture from dimethyl propanedioate was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue was treated with water (75.0ml). Addition of methylene chloride (100ml) to the red solution caused a red solid to precipitate which was collected to afford the sodium salt of dimethyl 2-(3-nitropyrid-2-yl)propanedioate (3.8g), m.p.224°. A solution of this salt in water (25.0ml) was acidified with concentrated hydrochloric acid and the precipitated solid collected to afford dimethyl 2-(3-nitropyrid-2-yl)propanedioate (102b) (2.3g, 18%) which formed colourless plates, m.p. 64-66° (from ethanol), ν_{max} 1750-1730 (C=O) and 1530 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.79 (1H, dd, J = 5 and 2 Hz, ArH), 8.46 (1H, dd, J = 8 and 2 Hz, ArH), 7.50 (1H, dd, J = 8 and 5 Hz, ArH), 5.54 (1H, s, CH) and 3.79 (6H, s, 2 x CH_3).

Acidification of the original two phase mother liquor followed by extraction with methylene chloride (3 x 100ml) gave a red oil which was triturated with ethanol to give a solid, which was combined with a second crop obtained by rotary evaporation of the organic mother liquor and flash-chromatography of the residue in hexane-ethyl acetate (9:1) over silica, to afford more dimethyl 2-(3-nitropyrid-2-yl)propanedioate (102b) (total 6.7g, 53%) as a yellow solid, m.p. 62-65°, identical (m.p. and i.r. spectrum) to an authentic sample.

(iii) Di-*tert*-butyl 2-(3-Nitropyrid-2-yl)propanedioate (102c)

The mixture from di-*tert*-butyl propanedioate was diluted with water (25.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue was treated with water (75.0ml). The mixture was then extracted with methylene chloride to give an orange oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (5:1) gave unreacted di-*tert*-butyl propanedioate (48%) identical [i.r. spectrum and t.l.c in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

Further elution with hexane-ethyl acetate (5:1) afforded di-*tert*-butyl 2-(3-nitropyrid-2-yl)propanedioate (102c) (78%) which formed colourless prisms, m.p. 65-66° [from light petrol (b.p. 40-60°], ν_{max} 1745-1730 (C=O) and 1530 and 1345 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.74 (1H, dd, J = 5 and 2 Hz, ArH), 8.38 (1H, dd, J = 8 and 2 Hz, ArH), 7.44 (1H, dd, J = 8 and 5 Hz, ArH), 5.29 (1H, s, CH) and 1.45 (18H, s, 6 x CH_3).

Final elution with methanol gave a red oil whose i.r. spectrum showed it to be mainly dimethylformamide.

(iv) Dibenzyl 2-(3-Nitropyrid-2-yl)propanedioate (102d)

The mixture from dibenzyl propanedioate was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue was treated with water (75.0ml). The resulting solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride to give a red oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted dibenzyl propanedioate (50%) as a yellow oil identical [i.r. spectrum and t.l.c in hexane-ethyl acetate (7:3) over silica] to an authentic sample.

Elution with hexane-ethyl acetate (7:3) afforded dibenzyl 2-(3-nitropyrid-2-yl)propandioate (102d) (94%) which formed colourless, irregular crystals, m.p. 87-88° (from ethanol), ν_{max} 1747 and 1729 (C=O) and 1528 and 1346 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.74 (1H, dd, J = 5 and 2 Hz, ArH), 8.43 (1H, dd, J = 8 and 2 Hz, ArH), 7.46 (1H, dd, J = 8 and 5 Hz, ArH), 7.31 (10H, s, 10 x ArH), 5.67 (1H, s, CH) and 5.26 (4H, s, 2 x CH_2).

Final elution with methanol gave a red oil from which no identifiable material was obtained.

(v) Ethyl 2-(3-Nitropyrid-2-yl)-3-oxobutanoate (105a)

The mixture from ethyl 3-oxobutanoate was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue was treated with water (75.0ml). The resulting solution was acidified with concentrated sulphuric acid and extracted with methylene chloride to give a brown oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a series of yellow oils (total = 2.8g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed them to contain mainly unreacted ethyl 3-oxobutanoate.

Further elution with hexane-ethyl acetate (9:1) afforded ethyl 2-(3-nitropyrid-2-yl)-3-oxobutanoate (105a) (7.8g; 62%) as an orange oil, b.p. 95°/ 0.05mmHg, ν_{max} 1740-1720 and 1650-1630 (C=O) and 1525 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.84-8.72 (1H, m, ArH), 8.51-8.21 (1H, m, ArH), 7.56-7.32 (1H, m, ArH), 4.40-4.01 (3H, m) and 2.47-1.07 (6H, m),δ_C ($CDCl_3$) 176.2 (quat), 170.1 (quat), 168.9 (quat), 166.8 (quat), 152.8 (CH), 152.3 (CH), 149.8 (quat), 149.4 (quat), 145.4 (quat), 144.7 (quat), 133.1 (CH), 132.8 (CH), 132.1 (CH), 123.5 (CH), 123.1 (CH), 122.6 (CH), 101.8 (quat), 65.4 (CH), 61.8 (CH_2), 61.1 (CH_2), 60.8 (CH_2), 43.0 (CH_2), 29.9 (CH_3), 19.7 (CH_3), 13.8 (CH_3) ,13.7 (CH_3) and 13.5 (CH_3).

Final elution with methanol gave only an intractable brown oil which was not further investigated.

(vi) Ethyl 2-(3-Nitropyrid-2-yl)-3-oxo-3-phenylpropanoate (105b)

The mixture from ethyl 3-oxo-3-phenylpropanoate was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (75.0ml). The resulting solution was acidified with 2M aqueous hydrochloric acid then extracted with methylene chloride (3 x 100ml) to give a red oil (26.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted ethyl 3-oxo-3-phenylpropanoate (8.0g; 38%) as a yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (2:1) over silica] to an authentic sample.

Further elution with hexane-ethyl acetate (9:1) gave a series of multicomponent oils (total 4.3g) which were not further investigated.

Further elution with hexane-ethyl acetate (9:1) followed by hexane-ethyl acetate (4:1) afforded ethyl 2-(3-nitropyrid-2-yl)-3-oxo-3-phenylpropanoate (105b) (10.7g; 68%) as an orange oil, ν_{max} 1750-1730 and 1700-1680 (C=O) and 1525-1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.68 (1H, dd, J = 5 and 2 Hz, ArH), 8.42 (1H, dd, J = 8 and 2 Hz, ArH), 7.90 (2H, dd, J = 7 and 2 Hz, 2 x ArH), 7.55-7.15 (4H, m, 4 x ArH), 6.48 (1H, s, CH), 4.24 (2H, q, J = 7 Hz, CH_2) and 1.75 (3H, t, J = 7 Hz, CH_3), which could not be further purified by high vacuum distillation due to its thermal instability.

Final elution with methanol gave an intractable brown gum (2.2g) which was not further investigated.

(vii) Ethyl 2-Cyano-2-(3-nitropyrid-2-yl)ethanoate (105d)

The mixture from ethyl 2-cyanoethanoate was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue

treated with water (75.0ml). The resulting solution was acidified with concentrated hydrochloric acid and the precipitated solid collected to afford ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (93%) which formed orange needles, m.p.135-136° (from ethyl acetate) (lit.[44] 136-137°), ν_{max} 2190 (CN), 1631 (C=O) and 1529 and 1334 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.92 (1H, dd, J = 5 and 2 Hz, ArH), 8.56 (1H, dd, J = 9 and 2 Hz, ArH), 7.65 (1H, dd, J = 9 and 5 Hz, ArH), 5.88 (1H, s, CH), 4.32 (2H, q, J = 7.1 Hz, CH_2) and 1.33 (3H, t, J = 7.1 Hz, CH_3), $\delta_H[(CD_3)_2S=O]$ 8.48-8.34 (2H, m, 2 x ArH), 7.00 (1H, dd, J = 7.7 and 6.4 Hz, ArH), 4.21 (2H, q, J = 7.1 Hz, CH_2) and 1.24 (3H, t, J = 7.1 Hz, CH_3), $\delta_C[(CD_3)_2S=O]$ 168.4 (quat), 146.3 (quat), 142.1 (CH), 140.1 (quat), 138.9 (quat), 116.3 (quat), 112.3 (CH), 61.2 (quat), 60.2 (CH_2) and 14.4 (CH_3).

Extraction of the aqueous mother liqour with methylene chloride gave a multicomponent red oil which was not further investigated.

(vii) Ethyl 2-Benzenesulphonyl-2-(3-nitropyrid-2-yl)ethanoate (105e)

The mixture from ethyl 2-benzenesulphonylethanoate was diluted with water (25.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (75.0ml). The resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give a red oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) and then with hexane-ethyl acetate (7:3) gave only a series of multicomponent oils and solids which were not further investigated.

Elution with hexane-ethyl acetate (3:2) afforded ethyl 2-benzenesulphonyl-2-(3-nitropyrid-2-yl)ethanoate (105e) (26%) which formed colourless, irregular crystals, m.p. 148-149° (from toluene), ν_{max} 1723 (C=O) and 1530 and 1343 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.77 (1H, dd, J = 5 and 2 Hz, ArH), 8.40 (1H, dd, J =

8 and 2 Hz, ArH), 7.91-7.46 (7H, m, 6 x ArH and CH), 4.19 (2H, q, J = 7 Hz, CH_2) and 1.16 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (3:2) afforded 2-benzenesulphonylethanoic acid (13%) which formed colourless plates, m.p. 111-112° (from toluene) (lit.[119] 112-114°), ν_{max} 3500-2500 br (OH) and 1728 and 1666 (C=O) cm^{-1}, δ_H [$(CD_3)_2S=O$] 7.94-7.91 (5H, m, 5 x ArH), 4.50 (2H, s, CH_2) and 3.33 (1H, bs, OH) (exch.).

Final elution with methanol gave an intractable black oil which was not further investigated.

(viii) Benzyl Ethyl 2-(3-Nitropyrid-2-yl)propanedioate (118)

The mixture from benzyl ethyl propanedioate was diluted with water (25.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (75.0ml). The resulting solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride to give a yellow oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted benzyl ethyl propanedioate (49%) as a yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] to an authentic sample.

Elution with hexane-ethyl acetate (3:1) afforded benzyl ethyl 2-(3-nitropyrid-2yl)propanedioate (118) (90%) as a pale orange oil, ν_{max} 1755 and 1740 (C=O) and 1530 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.76 (1H, dd, J = 5 and 2 Hz, ArH), 8.44 (1H, dd, J = 8 and 2 Hz, ArH), 7.47 (1H, dd, J = 8 and 5 Hz, ArH), 7.33 (5H, m, 5 x ArH), 5.60 (1H, s, CH), 5,28 (2H, s, CH_2), 4.27 (2H, q, J = 7 Hz, CH_2) and 1.23 (3H, t, J = 7 Hz, CH_3), which could not be further purified by high vacuum distillation due to its thermal instability.

Final elution with methanol gave a multicomponent oil which was not further investigated.

Attempted Pyrolyses of Diethyl 2-(3-Nitropyrid-2-yl)propanedioate (102a)

(a) Diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) was heated at 110-120° (oil bath) under high vacuum (0.3mmHg) in a cold-finger apparatus for 15min.

Unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.46g; 88%) was obtained as a yellow sublimate, m.p. 61-64°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) in anhydrous toluene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture gave unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

(c) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in anhydrous xylene (50.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 120h.

Rotary evaporation of the mixture gave a brown gum (3.1g) whose t.l.c in hexane-ethyl acetate (1:1) over silica showed it to contain mainly unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a).

(d) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (90.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave a brown oil which was triturated with hexane to give unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.2g; 86%) as a yellow solid, m.p. 54-57°, identified by comparison (m.p. and i.r. spectrum) to an authentic sample

Rotary evaporation of the organic mother liquor gave only a complex, orange gum (0.16g) which was not further investigated.

Pyrolyses of Diethyl 2-(3-Nitropyrid-2-yl)propanedioate (102a)

(a) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in anhydrous xylene (50.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture gave a dark brown gum (1.7g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.08g; 3%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Further elution with hexane-ethyl acetate (9:1) gave a multicomponent orange oil (0.27g) which was not further investigated.

Further elution with hexane-ethyl acetate (9:1) afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (1.1g; 52%) as an orange oil, b.p. 120-125°/ 1.6mmHg, ν_{max} 1740 (C=O) and 1530 and 1350 NO_2) cm $^{-1}$, δ_H ($CDCl_3$) 8.74 (1H, dd, J = 5 and 2 Hz, ArH), 8.37 (1H, dd, J = 8 and 2 Hz, ArH), 7.43 (1H, dd, J = 8 and 5 Hz, ArH), 4.28 (2H, q, J = 7 Hz, CH_2) and 1.21 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (1:1) afforded ethyl isoxazolo

[4,3-b]pyridine-3-carboxylate (103a) (0.20g; 10%) which formed pale orange, irregular crystals, m.p. 100-102° (from hexane-ethyl acetate), ν_{max} 1735 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.82 (1H, dd, J = 4 and 2 Hz, ArH), 8.09 (1H, dd, J = 9 and 2 Hz, ArH), 7.29 (1H, dd, J = 9 and 4 Hz, ArH), 4.61 (2H, q, J = 7 Hz, CH_2) and 1.48 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (1:4) and then finally with methanol gave only a series of complex oils and gums (total = 0.07g) which were not further investigated.

(b) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) in anhydrous diglyme (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1.5h.

Rotary evaporation of the mixture gave a brown gum (0.64g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) through to ethyl acetate and then finally with methanol gave only a series of complex oils, gums and solids (total 0.49g) from which no identifiable material was obtained.

(c) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in 2,4,6-trimethylpyridine (10.0ml) was stirred and heated under reflux with exclusion of atmoapheric moisture for 24h.

Rotary evaporation of the mixture gave a black gum (1.9g) which was treated with 2M aqueous hydrochloric acid (5.0ml) and the resulting mixture was extracted with diethyl ether (4 x 20.0ml) to give a red oil (0.18g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which was therefore not further investigated.

Neutralisation of the aqueous phase with 2M aqueous sodium hydroxide followed glacial acetic acid and collection of the precipitated solid gave only an

intractable black solid (0.68g), m.p. $>360^{o}$ from which no identifiable material could be obtained.

Extraction of the aqueous mother liquor with methylene chloride (3 x 25.0ml) gave only a multicomponent red oil (0.30g) which was not further investigated.

(d) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) and powdered sodium hydroxide (0.20g; 0.005mol) in Analar pyridine (5.0ml) was heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave a black gum which was treated with water (5.0ml) and the black solution was neutralised by addition of concentrated hydrochloric acid followed by solid sodium acetate then extracted with methylene chloride (3 x 50.0ml) to give a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.19g; 18%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:10 over silica] to a sample prepared previously.

Further elution with hexane-ethyl acetate (4:1) and then finally with methanol gave only a series of intractable oils and gums (0.18g) which were not further investigated.

(e) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (5.6g; 0.02mol) in anhydrous xylene (100ml) was stirred and heated under reflux for 24h with distillation of the solvent through a 20cm vigreux column and with addition of fresh anhydrous xylene when necessary.

Rotary evaporation of the mixture gave a gummy brown solid which was crystallised from hexane-toluene to afford ethyl isoxazolo[4,3-b]pyridine-3-

carboxylate (103a) (2.0g; 52%) as an orange solid, m.p. 98-100°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the organic mother liquor afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.45g; 11%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(f) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (50.0ml) was treated with anhydrous molecular sieves 5A (30g) and the resulting mixture was heated under reflux with exclusion of atmospheric moisture for 72h.

Elution with hexane-ethyl acetate (4:1) afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.40g; 38%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) afforded ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) as an orange solid (0.50g; 52%), m.p. 99-101°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a negligible amount of material.

Ethyl Isoxazolo[4,3-b]pyridine-3-carboxylate (103a)

(a) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

The mixture was rotary evaporated to afford ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.38g; 100%) as a brown solid, m.p. 93-100°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(b) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) in anhydrous dimethylformamide (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave a black gum (0.47g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) gave a complex brown oil (0.04g) followed by a multicomponent brown solid (0.05g) which were not further investigated.

Elution with hexane-ethyl acetate (1:1) afforded ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) (0.03g; 8%) as a brown solid, m.p. 100-103°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ethyl acetate (3:7) then finally with methanol gave only a series of multicomponent oils and gums (total 0.25g) which were not further investigated.

(c) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (0.56g; 0.002mol) in anhydrous pyridine (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 32h.

The mixture was diluted with 2M aqueous hydrochloric acid (50.0ml) and was extracted with methylene chloride (3 x 50.0ml) to afford ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) (0.11g; 29%) as a brown solid, m.p. 90-95°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(d) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in anhydrous xylene (50.0ml) was stirred and heated under reflux for 24h using a 20cm vigreux column in such a way that any ethanol produced would distil over without distillation of the xylene.

Rotary evaporation of the mixture gave ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (1.8g; 95%) as a pale brown solid, m.p. 100-104°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(e) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (90.0ml) was stirred and heated under reflux for 24h while a steady stream of nitrogen was bubbled through the reaction mixture.

Rotary evaporation of the reaction mixture afforded ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) (0.83g; 87%) as a brown solid, m.p. 96-99°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(f) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous calcium chloride (15.0g) for 24h.

Rotary evaporation of the mixture gave a brown oil (1.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) and then with hexane-ethyl acetate (4:1) gave a series of complex oils (total 0.79g) from which no identifiable material was obtained.

Further elution with hexane-ethyl acetate (4:1) afforded ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) (0.25g; 26%) as an orange solid, m.p. 85-90°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only an intractable brown gum (0.14g) which was not further investigated.

(g) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture afforded ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (1.0g; 100%) as a brown solid, m.p. 94-100^0, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(h) Repetition of the above reaction on a 0.3 molar scale afforded ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) in 95% yield.

(i) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (50.0ml) was treated with anhydrous 5A molecular sieves (1.0g) and the mixture was heated under reflux with exclusion of atmospheric moisture for 144h.

The molecular sieves were removed by filtration and the reaction mixture was rotary evaporated to afford ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.95g; 99%) as a pale brown solid, m.p. 90-93^o, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(j) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous xylene (120ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through an empty soxhlet extractor for 24h.

Rotary evaporation of the mixture gave a brown oil (1.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent orange oil (0.58g) which was not further investigated.

Elution with hexane-ethyl acetate (7:3) afforded ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.51g; 53%) as an orange solid, m.p. 95-100°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only an intractable brown gum (0.11g) which was not further investigated.

(k) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) and freshly sublimed *para*-benzoquinone (1.1g; 0.01mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture gave a brown gum (3.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted *para*-benzoquinone (0.40g; 36%) as a waxy brown solid identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Elution with hexane-ethyl acetate (7:3) afforded ethyl isoxazolo [4,3-b]pyridine-3-carboxylate (103a) (1.3g; 68%) as an brown solid, m.p. 98-101°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only an intractable black glass (0.50g) which was not further investigated.

Isoxazolo[4,3-b]pyridine-3-carboxylic Acid (103f)

A suspension of ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (3.8g; 0.02mol) in 2M aqueous sodium hydroxide (50.0ml) was heated under reflux for

1min then water (20.0ml) was added and the resulting mixture was heated under reflux for a further 1min by which time all the suspended solid had dissolved.

The mixture was then cooled and the precipitated solid collected to afford sodium isoxazolo[4,3-b]pyridine-3-carboxylate (103e) (1.4g; 38%) as a monohydrate which formed cream needles, m.p.295-300° (decomp.) (from ethanol-water), ν_{max} 3440 br (H_2O) and 1623 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 8.60 - 8.56 (1H, m, ArH), 8.08 (1H, dd; J = 9 and 1 Hz, ArH) and 7.33 (1H, dd, J = 9 and 4 Hz, ArH).

A suspension of sodium isoxazolo[4,3-b]pyridine-3-carboxylate monohydrate (103e) (1.3g; 0.0064mol) in 2M aqueous hydrochloric acid (10.0ml) was stirred at room temperature for 10 min and then was filtered to afford isoxazolo [4,3-b]pyridine-3-carboxylic acid (103f) (1.1g; 34%) which formed brown needles, m.p.168° (decomp.) (from glacial acetic acid), ν_{max} 3357-1899 br (OH) and 1705 (C=O) cm-1, δH [$(CD_3)_2S$=O] 8.83 (1H, dd, J = 4 and 2 Hz, ArH), 8.30 (1H, dd, J = 9 and 4 Hz, ArH), 7.50 (1H, dd, J = 9 and 4 Hz, ArH) and 5.95 (1H, bs, OH) (exch.).

Ethyl 2-(3-Nitropyrid-2-yl)ethanoate (104a)

(a) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 56h.

Rotary evaporation of the mixture gave a brown oil which was kugelrohr distilled to afford ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (1.7g; 81%) as a yellow oil, b.p.80- 90°/0.4mmHg, identical [i.r. specrtum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(b) A solution of ethyl 2-(3-nitropyrid-2-yl)-3-oxo-3-phenylpropanoate (105b) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 48h.

The mixture was rotary evaporated and the residue was dissolved in methylene chloride (50.0ml). The resulting solution was washed with 2M aqueous hydrochloric acid (10.0ml) and was rotary evaporated to give a red semi-solid (2.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a red oil which was kugelrohr-distilled to afford ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (1.4g; 69%) as an orange oil, b.p.150-156°/1.5mmHg, identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Further elution with hexane-ethyl acetate (9:1) and then finally with methanol gave only a four component oil (0.20g) which was not further investigated.

(c) A stirred suspension of sodium hydride (1.1g; 0.044mol) in anhydrous dimethylformamide (20.0ml) was cooled to 0° (ice-salt bath) and was treated dropwise with a solution of diethyl 3-oxopentane-1,5-dioate (8.9g; 0.044mol) in anhydrous dimethylformamide (10.0ml). The resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated dropwise with a solution of 2-chloro-3-nitropyridine (3.2g; 0.02mol) in anhydrous dimethylformamide (10.0ml) and the resulting solution was stirred and heated at 100° (oil-bath) for 1h.

The mixture was diluted with water (10.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (25.0ml). The resulting solution was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3 x 50.0ml) to give a red oil (13.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a multicomponent yellow oil (5.5g) which was not further investigated.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (3.8g; 91%) as an orange oil, identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] to a sample prepared previously.

Final elution with methanol gave a complex brown oil (3.3g) which was not further investigated.

Methyl Isoxazolo[4,3-b]pyridine-3-carboxylate (103b)

(a) A solution of dimethyl 2-(3-nitropyrid-2-yl)propanedioate (102b) (1.3g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux for 12h using a 20cm vigreux column in such a way that any methanol produced would distil over without distillation of the xylene.

Rotary evaporation of the mixture afforded methyl isoxazolo[4,3-b]pyridine-3-carboxylate (103b) (0.89g; 100%) which formed brown plates, m.p. 137-139° (from hexane-toluene), ν_{max} 1720-1700 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.81 (1H, dd, J = 4 and 2 Hz, ArH), 8.08 (1H, dd, J = 9 and 2 Hz, ArH), 7.30 (1H, dd, J = 9 and 4 Hz, ArH) and 4.10 (3H, s, CH_3).

(b) A solution of dimethyl 2-(3-nitropyrid-2-yl)propanedioate (102b) (1.3g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture gave a brown solid (0.88g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) gave a multicomponent yellow oil (0.16g) which was not further investigated.

Further elution with hexane-ethyl acetate (1:1) afforded methyl isoxazolo[4,3-b]pyridine-3-carboxylate (103b) (0.69g; 78%), m.p. 133-137°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave no further material.

Pyrolysis Reactions of Di-*tert*-butyl 2-(3-Nitropyrid-2-yl)propanedioate (102c)

(a) A solution of di-*tert*-butyl 2-(3-nitropyrid-2-yl)propoanedioate (102c) (1.4g; 0.004mol) in anhydrous xylene (20.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture gave a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted di-*tert*-butyl 2-(3-nitropyrid-2-yl)propanedioate (102c) (0.66g; 47%) as a colourless solid, m.p. 56-59°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (9:1) gave only a multicomponent colourless oil (0.37g) which was not further investigated.

Further elution with hexane-ethyl acetate (9:1) afforded *tert*-butyl 2-(3-nitropyrid-2-yl)ethanoate (104c) (0.20g; 21%) as a colourless oil, b.p. 110°/1.0 mmHg, ν_{max} 1730 (C=O) and 1530 and 1350 cm^{-1}, δ_H ($CDCl_3$) 8.75 (1H, dd, J = 5 and 2 Hz, ArH), 8.38 (1H, dd, J = 8 and 2 Hz, ArH), 7.42 (1H, dd, J = 8 and 5 Hz, ArH), 4.23 (2H, s, CH_2) and 1.41 (9H, s, 3 x CH_3).

Elution with hexane-ethyl acetate (4:1) afforded *tert*-butyl isoxazolo [4,3-b]pyridine-3-carboxylate (103c) (0.10g; 11%) which formed colourless, irregular crystals, m.p. 126-127° (from ethanol), ν_{max} 1715 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.78 (1H, dd, J = 4 and 2 Hz, ArH), 8.05 (1H, dd, J = 9 and 2 Hz, ArH), 7.28 (1H, dd, J = 9 and 4 Hz, ArH) and 1.68 (9H, s, 3 x CH_3).

Final elution with methanol gave a negligible amount of material.

(b) A solution of di-*tert*-butyl 2-(3-nitropyrid-2-yl)propanedioate (102c) (1.4g; 0.004mol) in anhydrous xylene (20.0ml) was stirred and heated under reflux for 24h using a 20cm vigreux column in such a way that any *tert*-butanol produced would distil over without distillation of the xylene.

Rotary evaporation of the mixture gave a brown gum (0.85g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded *tert*-butyl 2-(3-nitropyrid-2-yl)ethanoate (104c) (0.09g; 9%) as a yellow oil, identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (4:1) afforded *tert*-butyl isoxazolo [4,3-b]pyridine-3-carboxylate (103c) (0.39g; 44%), m.p. 120-125°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a complex brown glass (0.19g) which was not further investigated.

(c) A solution of di-*tert*-butyl 2-(3-nitropyrid-2-yl)propoanedioate (102c) (1.4g; 0.004mol) in anhydrous xylene (120ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through an empty soxhlet extractor for 24h.

Rotary evaporation of the mixture gave a brown oil (1.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a series of multicomponent oils (total 0.23g) which were not further investigated.

Further elution with hexane-ethyl acetate (9:1) afforded *tert*-butyl 2-(3-nitropyrid-2-yl)ethanoate (104c) (0.33g; 35%) as an orange oil identical [i.r.

spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (4:1) afforded *tert*-butyl isoxazolo [4,3-b]pyridine-3-carboxylate (103c) (0.48g; 50%), m.p. 116-123°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Further elution with hexane-ethyl acetate (4:1) and then finally with methanol gave a series of multicomponent oils and gums (total 0.50g) which were not further investigated.

tert-Butyl Isoxazolo[4,3-b]pyridine-3-carboxylate (103c)

A solution of di-*tert*-butyl 2-(3-nitropyrid-2-yl)propoanedioate (102c) (1.2g; 0.0036mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture gave a brown oil (1.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a small amount of an orange oil (0.03g) which was not further investigated.

Further elution with hexane-ethyl acetate (9:1) afforded *tert*-butyl isoxazolo[4,3-b]pyridine-3-carboxylate (103c) (0.49g; 62%), m.p. 110-120°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a complex brown gum (0.19g) which was not further investigated.

Attempted Pyrolysis Reactions of Dibenzyl 2-(3-Nitropyrid-2-yl)propanedioate (102d)

(a) A solution of dibenzyl 2-(3-nitropyrid-2-yl)propanedioate (102d) (1.6g; 0.004mol) in anhydrous xylene (20.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave only unreacted dibenzyl 2-(3-nitropyrid-2-yl)propanedioate (102d) (1.4g; 88%) as a brown solid, m.p. 102-104°, identical (m.p. and i.r. spectrum) with an authentic sample.

(b) A solution of dibenzyl 2-(3-nitropyrid-2-yl)propanedioate (102d) (1.6g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture gave only unreacted dibenzyl 2-(3-nitropyrid-2-yl)propanedioate (102d) (1.5g; 94%) as a brown solid, m.p. 99-103°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Pyrolysis of Ethyl 2-(3-Nitropyrid-2-yl)-3-oxobutanoate (105a)

A solution of ethyl 2-(3-nitropyrid-2-yl)-3-oxobutanoate (105a) (1.0g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

Rotary evaporation of the mixture gave a brown gum (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a multicomponent yellow oil which was not further investigated.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-(3-nitropyrid-2-yl)-3-oxobutanoate (105a) (0.36g; 36%) identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (2:1) over silica] to an authentic sample.

Further elution with hexane-ethyl acetate (4:1) afforded 3-acetylisoxazolo[4,3-b]pyridine (106a) as an orange solid, m.p. 97-100°, ν_{max} 1660 (C=O) cm^{-1}.

Further elution with hexane-ethyl acetate (4:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and intractable tars (total 0.56g) from which no identifiable material was obtained.

3-Benzoylisoxazolo[4,3-b]pyridine (106b)

A solution of ethyl 2-(3-nitropyrid-2-yl)-3-oxo-3-phenylpropanoate (105b) (1.3g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 28h.

Rotary evaporation of the mixture gave a brown gum (1.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a series of multicomponent oils and gums (total 0.74g) from which no identifiable material was obtained.

Further elution with hexane-ethyl acetate (9:1) afforded 3-benzoylisoxazolo[4,3-b]pyridine (106b) which formed orange needles, m.p. 125-126° (from methanol), ν_{max} 1735-1715 (C=O) cm^{-1} , δ_H ($CDCl_3$) 8.84 (1H, dd, J = 4 and 1 Hz, ArH), 8.25-8.20 (1H, m, ArH), 8.15 (1H, dd, J = 9 and 1 Hz, ArH), 7.74-7.53 (4H, m, 4 x ArH) and 7.36 (1H, dd, J = 9 and 4 Hz, ArH)

Final elution with methanol gave no material.

Attempted Reactions of 2-Chloro-3-nitropyridine (101) with Diethyl 3-Oxopentane-1,5-dioate

A stirred suspension of sodium hydride (0.53g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl 3-oxopentane-1,5-dioate (4.4g; 0.022mol) in anhydrous dimethylformamide (5.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated with a solution of 2-chloro-3-nitropyridine (101) (1.6g; 0.01mol) in anhydrous dimethylformamide (5.0ml). The resulting red solution was stirred either at room temperature or at 50° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) The mixture from the reaction at room temperature was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (12.5ml). The suspended solid was collected to give only unreacted 2-chloro-3-nitropyridine (101) (1.4g; 88%) as a yellow solid, m.p. 98-100° (lit.,[120] 101-102°), identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3 x 100ml) to give unreacted diethyl 3-oxopentane-1,5-dioate (4.1g; 93%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

(ii) The mixture from the reaction at 50° was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated. The residue was treated with water (12.5ml)and the insoluble solid was collected to give only unreacted 2-chloro-3-nitropyridine (101) (1.4g; 88%) as a yellow solid, m.p. 95-

100° (lit.,[120] 101-102°), identified by comparison (m.p. and i.r. spectrum) to an authentic sample.

The aqueous mother liquor was acidified with concentrated hydrochloric acid and extracted with methylene chloride (3 x 20.0ml) to give unreacted diethyl 3-oxopentane-1,5-dioate (4.3g; 98%) as an yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

3-Cyanoisoxazolo[4,3-b]pyridine (106d)

(a) A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (0.47g; 0.002mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture gave a gummy, brown solid (0.32g). This was washed with diethyl ether to leave an insoluble, multicomponent brown solid (0.10g), m.p. 60-65°, which was not further investigated.

Rotary evaporation of the ethereal washings afforded 3-cyanoisoxazolo [4,3-b]pyridine (106d) (0.20g; 69%) which formed cream needles, m.p. 85-86° (from ethanol), ν_{max} 2240 (CN) cm^{-1}, δ_H ($CDCl_3$) 8.80 (1H, dd, J = 4 and 1 Hz, ArH), 8.14 (1H, dd, J = 9 and 1 Hz, ArH) and 7.39 (1H, dd, J = 9 and 4 Hz, ArH).

(b) A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (2.4g; 0.01mol) in anhydrous xylene (50.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 120h.

Rotary evaporation of the mixture gave a brown gum (2.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a multicomponent yellow oil (0.20g) which was not further investigated.

Elution with hexane-ethyl acetate (4:1) afforded 3-cyanoisoxazolo [4,3-b]pyridine (106d) (0.21g; 14%) as a yellow solid, m.p. 65-70°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Further elution with hexane-ethyl acetate (4:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and solids (total 1.7g) which were not further investigated.

(c) A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (5.6g; 0.025mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

Rotary evaporation of the mixture gave a brown solid (4.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded 3-cyanoisoxazolo [4,3-b]pyridine (106d) (3.0g; 83%) as a yellow solid, m.p. 77-82°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only an intractable brown tar (0.40g). which was not investigated.

2-(3-Nitropyrid-2-yl)ethanenitrile (107)

A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (2.4g; 0.01mol) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 10h.

The mixture was rotary evaporated and the residue was dissolved in methylene chloride (50.0ml) and the resulting solution was washed with 2M aqueous hydrochloric acid (10.0ml) and rotary evaporated to give a black gum (1.1g) which was flash-chromatographed over alumina.

Elution with hexane-ethyl acetate (4:1) afforded 2-(3-nitropyrid-2-yl)ethanenitrile (107) (0.59g; 36%) which formed pale yellow needles, m.p. 107-109° (from ethanol), ν_{max} 2254 (CN) and 1533 nad 1349 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.89 (1H, dd, J = 5 and 2 Hz, ArH), 8.49 (1H ,dd, J = 8 and 2 Hz, ArH), 7.58 (1H, dd, J = 8 and 5 Hz, ArH) and 4.43 (2H, s, CH_2).

Final elution with methanol gave an intractable black gum (0.31g) which was not further investigated.

The Attempted Pyrolysis of Ethyl 2-Benzenesulphonyl-2-(3-nitropyrid-2-yl)ethanoate (105e)

A solution of ethyl 2-benzenesulphonyl-2-(3-nitropyrid-2-yl)ethanoate (105e) (1.2g; 0.0035mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 72h.

Rotary evaporation of the mixture gave a dark brown gum (0.92g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent gums and solids (total 0.80g) from which no identifiable material was obtained.

3-Nitropyridin-4(1H)-one

3-Nitropyridin-4(1H)-one was prepared by the reaction of pyridin-4(1H)-one with fuming nitric acid and fuming sulphuric acid as described by Kruger and Mann[46] as a colourless solid (yield 79%), m.p. 284-286° (lit,.[46] 278-279°).

4-Chloro-3-nitropyridine (110)

4-Chloro-3-nitropyridine (110) was prepared by the reaction of 3-nitropyridin-4(1H)-one with phosphorus pentachloride as described by Kruger and Mann[46] as a yellow solid (yield 77%), m.p. 42-45° (lit,.[46] 45°).

Diethyl 2-(3-Nitropyrid-4-yl)propanedioate (111)

A stirred suspension of sodium hydride (7.6g; 0.32mol) in anhydrous dimethylformamide (150ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (50.4g; 0.32mol) in anhydrous dimethylformamide (75.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated with a solution of 4-chloro-3-nitropyridine (111) (23.8g; 0.15mol) in anhydrous dimethylformamide (75.0ml) and the resulting red solution was stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h.

The mixture was diluted with water (75.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (150ml). Addition of methylene chloride (100ml) followed by filtration of the resulting suspension gave a solid, which was combined with a second crop obtained by separation of the two phase mother liquor, extraction of the aqueous phase with methylene chloride (2 x 250ml) to give a red oil which was treated with 2M aqueous sodium hydroxide (150ml) and methylene chloride (250ml) followed by filtration of the resulting suspension, to afford the sodium salt of diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (32.7g) as a red solid, m.p. 65-70°. A solution of this salt in water (150ml) was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (3 x 150ml) to afford diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (32.6g; 74%) as a yellow oil, b.p. 90-100°/ 0.1mmHg, ν_{max} 1751 and 1735 (C=O) and 1532 and 1354 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.22 (1H, s,

ArH), 8.79 (1H, d, J = 5 Hz, ArH), 7.72 (1H, d, J = 5 Hz, ArH), 5.32 (1H, s, CH), 4.24 (4H, q, J = 7 Hz, 2 x CH_2) and 1.24 (6H, t, J = 7 Hz, 2 x CH_3).

Acidification of the combined alkaline aqueous phases with concentrated hydrochloric acid and extraction with methylene chloride gave more diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (9.7g; 23%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

The Pyrolysis of Diethyl 2-(3-Nitropyrid-4-yl)propanedioate (111)

A solution of diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (1.4g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 96h.

Rotary evaporation of the mixture gave a brown gum (1.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded ethyl isoxazolo [3,4-c]pyridine-3-carboxylate (112) (0.67g; 69%) which formed yellow needles, m.p. 79-80° (from hexane-toluene) ν_{max} 1715 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.44 (1H, d, J = 2 Hz, ArH), 8.28 (1H, d, J = 6 Hz, ArH), 7.73 (1H, dd, J = 6 and 2 Hz, ArH), 4.56 (2H, q, J = 7 Hz, CH_2) and 1.50 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (4:1) afforded ethyl 2-(3-nitropyrid-4-yl)ethanoate (113) (0.074g; 7%) as a yellow oil, b.p. 120-125°/ 0.2 mmHg, ν_{max} 1736 (C=O) and 1530 and 1353 cm^{-1}, δ_H ($CDCl_3$) 9.24 (1H, s, ArH), 8.73 (1H, d, J = 5 Hz, ArH), 7.30 (1H, d, J = 5 Hz, ArH), 4.15 (2H, q, J = 7 Hz, CH_2), 4.02 (2H, s, CH_2) and 1.22 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a neglible amount of material.

Ethyl 2-(3-Nitropyrid-4-yl)ethanoate (113)

A solution of diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (1.4g; 0.005mol) in pyridine (9.0ml) and water (1.0ml) was stirred and heated under reflux for 20h

The mixture was rotary evaporated and the residue was dissolved in methylene chloride (25.0ml) and the resulting solution washed with 2M aqueous hydrochloric acid (5.0ml) and rotary evaporated to afford ethyl 2-(3-nitropyrid-4-yl)ethanoate (113) (0.77g; 73%) as a yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] to a sample prepared previously.

The Attempted Pyrolysis of Ethyl 2-(3-Nitropyrid-2-yl)ethanoate (104a)

A solution of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.38g; 0.002mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture afforded unreacted ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.38g; 100%) as a red oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample prepared before.

The Pyrolysis of Benzyl Ethyl 2-(3-Nitropyrid-2-yl)propanedioate (118)

A solution of benzyl ethyl 2-(3-nitropyrid-2-yl)propanedioate (118) (1.4g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

Rotary evaporation of the mixture gave a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a series of multicomponent oils (total 0.07g) which were not further investigated.

Elution with hexane-ethyl acetate (4:1) gave a gummy solid which was crystallised from ethanol to afford dibenzyl 2-(3-nitropyrid-2-yl)propanedioate (102d) (0.15g; 13%) as cream plates, m.p. 100-102°, identified by comparison (m.p., combustion analysis and i.r., ^{1}H n.m.r and FAB mass spectra) with a sample prepared previously.

Elution with hexane-ethyl acetate (7:3) afforded benzyl isoxazolo [4,3-b]pyridine-3-carboxylate (103d) (0.54g; 53%) which formed pale yellow, irregular crystals, m.p. 128-130° (from ethanol), ν_{max} 1725 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.82 (1H, dd, J = 4 and 2 Hz, ArH), 8.08 (1H, dd, J = 9 and 2 Hz, ArH), 7.58-7.22 (6H, m, 6 x ArH) and 5.56 (2H, s, CH_2).

Final elution with methanol gave no further material.

Ethyl 4-Nitrophenyl Propanedioate

A stirred suspension of sodium hydride (1.2g; 0.05mol) in anhydrous 1,2-dimethoxyethane (30.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of 4-nitrophenol (7.0g;0.05mol) in anhydrous 1,2-dimethoxyethane (40.0ml) and the resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min. The mixture was then treated dropwise with a solution of ethyl malonyl chloride (7.5g; 0.05mol) in anhydrous 1,2-dimethoxyethane (30.0ml) and stirred at room temperature with exclusion of atmospheric moisture for 4h.

The mixture was rotary evaporated and the residue treated with anhydrous diethyl ether (100ml) to give a suspension which was filtered through celite. The organic filtrate was rotary evaporated to give a waxy solid which was crystallised from ethanol to give a solid, which was combined with a second crop obtained by rotary evaporation of the ethanolic mother liquor and flash-chromatography of the residue in hexane-methylene chloride (1:1) over silica, to afford ethyl 4-nitrophenyl

propanedioate (total 5.9g; 47%) as colourless crystals, m.p. 56-58° (lit.,[51] 60-60.5°), ν_{max} 1770 and 1725 (C=O) and 1530 and 1350 (NO_2) cm^{-1}.

The Attempted Reaction of 2-Chloro-3-nitropyridine (101) with Ethyl 4-Nitrophenyl Propanedioate

A stirred suspension of sodium hydride (0.53g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of ethyl 4-nitrophenyl propanedioate (5.6g; 0.022mol) in anhydrous dimethylformamide (5.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min and then was treated dropwise with a solution of 2-chloro-3-nitropyridine (1.6g; 0.01mol) in anhydrous dimethylformamide (5.0ml) and stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h.

The mixture was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (12.5ml). The resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (3 x 15.0ml) to give a red oil (7.9g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent yellow oil (0.16g) which was not further investigated.

Further elution with hexane-ethyl acetate (4:1) afforded 4-nitrophenol (3.0g; 100%) as a pale yellow solid, m.p. 87-94° (lit.,[121] 114°), identified by comparison [m.p., i.r. spectrum and t.l.c in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Final elution with methanol gave only a multicomponent red oil (1.6g) which was not further investigated.

Diethyl 2-(5-Nitropyrid-2-yl)propanedioate (121)

A stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (17.6g; 0.11mol) in anhydrous dimethylformamide (25.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated dropwise with a solution of 2-chloro- 5-nitropyridine (120) (7.9g; 0.05mol) in anhydrous dimethylformamide (25.0ml) and the resulting solution stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h.

The mixture was diluted with water (10.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (100ml). The precipitated solid was collected and combined with a second crop obtained by acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid followed by collection of the precipitated solid to give diethyl 2-(5-nitropyrid-2-yl)propanedioate (121) (total 11.4g; 81%) which formed a yellow microcrystalline solid, m.p. 73-75° [from light petroleum (b.p. 80-100°) - 1,2-dimethoxyethane] (lit.,[52] 97-99°), ν_{max} 1665 (C=O) and 1515 and 1355 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.34 (1H, dd, J = 3 and 1 Hz, ArH), 8.47 (1H, dd, J = 9 and 3 Hz, ArH), 7.73 (1H ,dd, J = 9 and 1 Hz, ArH), 5.03 (1H, s, CH), 4.24 (4H, q, J = 7 Hz, 2 x CH_2) and 1.25 (6H, t, J = 7 Hz, 2 x CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 100ml) gave an orange oil (9.7g) whose t.l.c. in hexane-diethyl ether (3:1) over silica showed it to contain mainly unreacted diethyl propanedioate.

The Pyrolysis of Diethyl 2-(5-Nitropyrid-2-yl)propanedioate (121)

A solution of diethyl 2-(5-nitropyrid-2-yl)propanedioate (121) (2.8g; 0.01mol) in anhydrous xylene (100ml) was stirred and heated under reflux with

exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

Rotary evaporation of the mixture gave a brown oil (2.8g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a multicomponent orange oil (0.33g) which was not further investigated.

Elution with hexane-ethyl acetate (17:3) gave an orange oil which was triturated with hexane-diethyl ether to give unreacted diethyl 2-(5-nitropyrid-2-yl)propanedioate (121) (0.23g; 9%) as a yellow solid identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (17:3) gave a red oil which was kugelrohr distilled to give 2-methyl-5-nitropyridine (123) (0.08g; 6%) as a yellow solid, m.p. 94-98° (lit.,[43] 108-110°), b.p. 60°/ 0.4mmHg, ν_{max} 1510 and 1355 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.32 (1H, d, J = 3 Hz ,ArH), 8.36 (1H, dd, J = 9 and 3 Hz, ArH), 7.34 (1H, d, J = 9 Hz, ArH) and 2.69 (3H, s, CH_3), followed by ethyl 2-(5-nitropyrid-2-yl)ethanoate (122) (0.34g; 16%) as an orange oil, b.p. 110°/ 0.4mmHg, ν_{max} 1731 (C=O) and 1523 and 1354 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.31 (1H, d, J = 3 Hz, ArH), 8.41 (1H, dd, J = 9 and 3 Hz, ArH), 7.50 (1H, d, J = 9 Hz, ArH) ,4.15 (2H, q, J = 7 Hz, CH_2), 3.94 (2H, s, CH_2) and 1.22 (3H, t, J = 7 Hz, CH_3), then a multicomponent brown oil (0.23g), b.p. 180-200°/ 0.4mmHg, which was not further investigated.

Elution with hexane-ethyl acetate (1:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and gums (total 0.93g) from which no identifiable material was obtained.

Ethyl 2-(5-Nitropyrid-2-yl)ethanoate (122)

A solution of diethyl 2-(5-nitropyrid-2-yl)propanedioate (121) (2.8g; 0.01mol) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 48h.

The mixture was rotary evaporated and the residue dissolved in methylene chloride (50.0ml) and the solution washed with 2M aqueous hydrochloric acid (10.0ml) and rotary evaporated to afford ethyl 2-(5-nitropyrid-2-yl)ethanoate (122) (1.4g; 67%) as an orange oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Diethyl Sodio 2-(3-Nitropyrid-2-yl)propanedioate (124)

A stirred suspension of sodium hydride (0.48g; 0.02mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was treated dropwise with a solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (5.6g; 0.02mol) in anhydrous 1,2-dimethoxyethane (10.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 1h.

Rotary evaporation of the mixture gave a gummy, red solid which was washed with anhydrous diethyl ether to afford diethyl sodio 2-(3-nitropyrid-2-yl)propanedioate (124) (5.2g; 86%) as a red solid, m.p. 212°, ν_{max} 3590, 3359, 3184, 1694 and 1660 (C=O) and 1523 and 1329 (NO_2) cm^{-1}.

The Attempted Pyrolysis of Diethyl Sodio 2-(3-Nitropyrid-2-yl)propanedioate (124) in Xylene

A solution diethyl sodio 2-(3-nitropyrid-2-yl)propanedioate (124) (1.5g; 0.005mol) in anhydrous xylene (25.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

The mixture was rotary evaporated and the residue was washed with diethyl ether to give unreacted diethyl sodio 2-(3-nitropyrid-2-yl)propanedioate (124) (1.2g;

80%) as a red solid, m.p. 200-206°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Rotary evaporation of the organic mother liquor gave a multicomponent brown oil (0.13g) which was not further investigated.

The Pyrolysis of Diethyl Sodio-2-(3-Nitropyrid-2-yl)propanedioate (124) in Diglyme

A solution diethyl sodio-2-(3-nitropyrid-2-yl)propanedioate (124) (1.5g; 0.005mol) in anhydrous diglyme (25.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated and the residue was washed with diethyl ether to give an insoluble brown solid (0.80g) which was dissolved in water (10.0ml) and the resulting solution acidified with glacial acetic acid and extracted with methylene chloride (3 x 25.0ml) to give a complex brown oil (0.29g) whose t.l.c. in hexane-ethyl acetate (7:3) over silica showed it to be a multicomponent mixture which was therefore not further investigated.

Rotary evaporation of the ethereal mother liquor gave a brown oil (0.43g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.32g; 30%) as a yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

Elution with hexane-ethyl acetate (3:2) afforded a colourless semi-solid which was tentatively identified as 2-(3-aminopyrid-2-yl)-2-oxoethanoic acid (125) (0.059g; 7%), b.p. 150°/ 1.0mmHg, ν_{max} 3417, 3279 and 3171 (NH), 3500-2500 br (OH), 1728 and 1693 (C=O) and 1625 (NH def.) cm^{-1}.

Final elution with methanol gave only a negligible amount of material.

2-Chloro-3-Nitropyridine-1-*N*-Oxide (126)

2-Chloro-3-nitropyridine-1-*N*-oxide (126) was prepared by the reaction of 2-chloro-3-nitropyridine (101) with trifluoroperacetic acid as described by Tortorella, Macioci and Poma[54] as a yellow solid (79%), m.p. 94-97° (lit.,[54] 99-100°).

Attempted Reactions of 2-Chloro-3-Nitropyridine-1-*N*-Oxide (126) with Diethyl Propanedioate

A stirred suspension of sodium hydride (0.53g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (3.5g; 0.022mol) in anhydrous dimethylformamide (5.0ml and the resulting mixture stirred at room temperature with exclusion of atmospheric moisture for 15min. The mixture was then treated with a solution of 2-chloro-3-nitropyridine-1-*N*-oxide (126) (1.75g; 0.01mol) in anhydrous dimethylformamide (5.0ml) and the resulting red solution was stirred either at room temperature or at 100° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) The mixture from the reaction at 100° was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (12.5ml). The resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (4 x 25.0ml) to give a red oil (5.8g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of complex, multicomponent oils and gums (total = 5.6g) from which no identifiable material could be obtained.

(ii) The mixture from the reaction at room temperature was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated and

the residue treated with water (12.5ml). The resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (3 x 25.0ml) to give a red oil (5.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of complex, multicomponent oils and gums (total 4.5g) from which no identifiable material could be obtained.

Diethyl 2-Hydroxy-2-(3-Nitropyrid-2-yl)propanedioate (128)

(a) A stirred mixture of 90% w/w aqueous hydrogen peroxide (0.40ml) and anhydrous methylene chloride (10.0ml) was cooled to 0-5° (ice bath) and treated in two portions with triflouroacetic anhydride (2.6ml) and the stirred solution then allowed to warm to room temperature. A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in anhydrous methylene chloride (10.0ml) was then added dropwise and the resulting mixture stirred at room temperature for 4h then heated under reflux for 2h and finally stirred at room temperature with exclusion of atmospheric moisture for a further 17h.

The mixture was rotary evaporated and the residue was treated with ice (8.0g) and the mixture basified with 10%w/v aqueous sodium hydrogen carbonate and extracted with methylene chloride (5 x 50.0ml) to give a yellow oil (3.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent yellow oil (0.28g) which was not further investigated.

Further elution with hexane-ethyl acetate (4:1) afforded diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (2.2g; 73%) which formed colourless, irregular crystals, m.p. 57-58° [from light petroleum (b.p. 40-60°) - toluene], ν_{max} 3470 (OH), 1755 and 1743 (C=O) and 1536 and 1372 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.70 (1H, dd, J = 4 and 2 Hz, ArH), 8.29 (1H, dd, J = 8 and 2 Hz, ArH), 7.53

(1H, dd, J = 8 and 4 Hz, ArH), 4.83 (1H, bs, OH) (exch.), 4.33 (2H, q, J = 7 Hz, CH_2), 4.33 (2H, q, J = 7 Hz, CH_2) and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

Elution with hexane-ethyl acetate (1:1) and then finally with methanol gave only a multicomponent yellow oil (0.74g) from which no identifiable material was obtained.

(b) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (14.1g; 0.05mol) in glacial acetic acid (125ml) was treated with 30%w/w aqueous hydrogen peroxide solution (62.5ml) and the resulting solution was stirred and heated at 50° (oil bath) for 24h.

The mixture was rotary evaporated to one half of the original volume then diluted with water (100ml) and made basic by the addition of solid sodium hydrogen carbonate. The resulting mixture was extracted with methylene chloride (3 x 250ml) and the extracts washed with saturated aqueous sodium thiosulphate solution (100ml) and rotary evaporated to afford diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (13.0g; 87%) as a pale yellow solid, m.p. 53-55°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(c) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.1g; 0.004mol) in 1M aqueous sodium hydroxide (10.0ml) was treated with 30%w/w aqueous hydrogen peroxide solution (2.0ml) and the resulting solution was stirred at room temperature for 2h.

The mixture was acidified with 2M aqueous hydrochloric acid and was extracted with methylene chloride (3 x 50.0ml) to give a yellow oil (0.83g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.76g; 63%) as a viscous, yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

Final elution with methanol gave no material.

(d) A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous acetonitrile (25.0ml) was treated with activated manganese dioxide (2.5g) and the resulting suspension was stirred at room temperature with exclusion of atmospheric moisture for 37h.

The mixture was filtered through celite and the filtrate rotary evaporated to afford a yellow oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (7:3) afforded diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.87g; 58%) as a colourless solid, m.p. 52-55°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with diethyl ether and then finally with methanol gave only an unidentified yellow solid (0.035g), m.p. 120-123° (decomp.).

The Attempted Acetylation of Diethyl 2-Hydroxy-2-(3-Nitropyrid-2-yl)propanedioate (128)

A stirred solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.30g; 0.001mol) in acetic anhydride (2.5ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated and the residue treated with water (2.5ml) to give a solution which was extracted with methylene chloride (3 x 5.0ml) to give only unreacted diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.29g; 97%) as an orange gum identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared before.

Diethyl 2-Methoxy-2-(3-Nitropyrid-2-yl)propanedioate (129)

A stirred suspension of sodium hydride (0.053g; 0.0022mol) in anhydrous dimethylformamide (2.5ml) was treated dropwise with a solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.60g; 0.002mol) in anhydrous dimethylformamide (5.0ml). The resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15 min and then was treated dropwise with a solution of methyl iodide (0.28g; 0.002mol) in anhydrous dimethylformamide (2.5ml) and the resulting solution stirred at room temperature with exclusion of atmospheric moisture for 24h.

The mixture was diluted with water (2.5ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (10.0ml). Extraction of the mixture with methylene chloride (3 x 20.0ml) afforded a brown oil which was purified by kugelrohr distillation to give diethyl 2-methoxy-2-(3-nitropyrid-2-yl)propanedioate (129) as a cream, crystalline solid (0.57g; 92%), m.p. 44-46°, b.p. 140-144°/ 0.1-0.3mmHg, ν_{max} 1756 and 1745 (C=O) and 1537 and 1364 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.67 (1H, dd, J =5 and 2 Hz, ArH), 8.13 (1H, dd, J = 8 and 2 Hz, ArH), 7.45 (1H, dd, J = 8 and 5 Hz, ArH), 4.33 (4H, q, J = 7 Hz, 2 x CH_2), 3.65 (3H, 2, CH_3) and 1.26 (6H, t, J = 7 Hz, 2 x CH_3).

The Attempted Pyrolysis of Diethyl 2-Hydroxy-2-(3-Nitropyrid-2-yl)propanedioate (128)

A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (1.5g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

The mixture was rotary evaporated to give unreacted diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (1.4g; 93%) as a pale yellow solid, m.p. 54-56°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

The Attempted Reaction of Meldrum's Acid with 2-Chloro-3-nitropyridine (101)

A stirred suspension of sodium hydride (0.53g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of Meldrum's Acid (3.2g; 0.022mol) in anhydrous dimethylformamide (5.0ml). The resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated with a solution of 2-chloro-3-nitropyridine (101) (1.6g; 0.01mol) in anhydrous dimethylformamide (5.0ml). The resulting red solution was stirred either at room temperature or at 100° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) The mixture from the reaction at 100° was diluted with water (5.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (25.0ml). The insoluble solid was collected to give unreacted 2-chloro-3-nitropyridine (101) (0.95g; 59%) as a yellow solid, m.p. 100-104° (lit.,[120] 101-102°) identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Neutralisation of the aqueous mother liquor by addition of concentrated hydrochloric acid followed by solid sodium acetate precipitated a brown solid which was collected but was found to decompose rapidly into an intractable black solid on drying under high vacuum at room temperature.

Extraction of the aqueous mother liquor with methylene chloride (3 x 100ml) gave a multicomponent brown oil (1.6g) which was not further investigated.

(ii) The mixture from the reaction at room temperature was diluted with water (5.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (25.0ml). The insoluble solid was collected to give unreacted 2-chloro-3-nitropyridine (101) (1.4g; 88%) as a yellow solid, m.p. 105-107° (lit.,[120] 101-102°) identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and then extraction with methylene chloride (3 x 50.0ml) gave unreacted Meldrum's Acid (2.9g; 91%) as a yellow solid, m.p. 95-98° (lit.,[122] 97°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Ethyl 2-Diazoethanoate

A sample of ethyl 2-diazoethanoate was kindly supplied by Dr. M. Davison, Department of Chemistry, University of Edinburgh.

Ethyl 2-Diazo-3-(3-nitropyrid-2-yl)-3-oxopropanoate (134)

Ethyl 2-diazoethanoate (1.1g; 0.01mol) was stirred and cooled to 10° (ice bath) then treated in one portion with 3-nitropyridine-2-carboxylic acid chloride (133) (0.93g; 0.005mol) and the resulting mixture was stirred at 10° for 10 min then heated at 50° (oil bath) for 18h.

The mixture was rotary evaporated to give a brown oil (1.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded ethyl 2-diazo-3-(3-nitropyrid-2-yl)-3-oxopropanoate (134) (0.73g; 57%) which formed pale yellow, irregular crystals, m.p. 86-87° (from ethanol), ν_{max} 2156 ($C=\overset{+}{N}=\overset{-}{N}$), 1716 and 1651(C=O) and 1531 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.85 (1H, dd, J =5 and 2 Hz, ArH), 8.50 (1H, dd, J = 8 and 2 Hz, ArH), 7.57 (1H, dd, J = 8 and 5 Hz, ArH), 4.11 (2H, q, J = 7 Hz, CH_2) and 1.14 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

The Pyrolysis of Ethyl 2-Diazo-3-(3-nitropyrid-2-yl)-3-oxopropanoate (134)

A solution of ethyl 2-diazo-3-(3-nitropyrid-2-yl)-3-oxopropanoate (134) (0.32g; 0.0012g) in anhydrous toluene (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

The mixture was rotary evaporated to give a brown gum (0.28g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent brown oil (0.07g) which was not further investigated.

Elution with hexane-ethyl acetate (7:3) afforded ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.05g; 23%) as an orange solid, m.p. 94-99°, identified by comparison (m.p., mixed m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) and then finally with methanol gave only a series of multicomponent gums (total 0.10g) which were not further investigated.

5-Chloro-1-ethyl-2-methyl-4-nitroimidazole

A sample of 5-chloro-1-ethyl-2-methyl-4-nitroimidazole was kindly supplied by Mr. C. McBride, Department of Chemistry, University of Edinburgh.

5-Cyano-1-ethyl-2-methyl-4-nitroimidazole

5-Cyano-1-ethyl-2-methyl-4-nitroimidazole was prepared by the reaction of 5-chloro-1-ethyl-2-methyl-4-nitroimidazole with pottasium cyanide as described by Sarasin and Wegmann[123] as a cream solid (yield 79%), m.p. 49-50° (lit.,[123] 70-71°), ν_{max} 2236 (CN), and 1514 and 1341 (NO_2) cm^{-1}.

1-Ethyl-2-methyl-4-nitroimidazole-5-carboxylic Acid

1-Ethyl-2-methyl-4-nitroimidazole-5-carboxylic acid was prepared by the reaction of 5-cyano-1-ethyl-2-methyl-4-nitroimidazole with concentrated sulphuric acid followed by aqueous sodium nitrite as described by Mann and Porter[124] as a colourless solid (yield 32%), m.p. 140-143° (decomp.) (lit.,[124] 139-141°), ν_{max} 1735 (C=O) and 1516 and 1346 (NO_2) cm^{-1}.

1-Ethyl-2-methyl-4-nitroimidazole-5-carboxylic Acid Chloride (136)

1-Ethyl-2-methyl-4-nitroimidazole-5-carboxylic acid chloride (136) was prepared by the reaction of 1-ethyl-2-methyl-4-nitroimidazole-5-carboxylic acid with thionyl chloride as described by Mann and Porter[124] as a golden oil (yield 100%), ν_{max} 1749 and 1714 (C=O) and 1540 and 1345 (NO_2) cm^{-1}.

Ethyl 2-Diazo-3-(1-ethyl-2-methyl-4-nitroimidazol-5-yl)-3-oxopropanoate (137)

Ethyl 2-diazoethanoate (2.2g; 0.02mol) was stirred and cooled to 10° (ice bath) then treated in one portion with 1-ethyl-2-methyl-4-nitroimidazole-5-carboxylic acid chloride (136) (2.3g; 0.01mol) and the resulting mixture was stirred at 10° for 10 min and then heated at 50° for 24h.

The mixture was rotary evaporated to give an orange oil (3.7g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-diazoethanoate (0.35g; 15%) as a yellow oil identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

Elution with hexane-ethyl acetate (1:1) afforded ethyl 2-diazo-3-(1-ethyl-2-methyl-4-nitroimidazol-5-yl)-3-oxopropanoate (137) (1.8g; 62%) which formed cream, irregular crystals, m.p. 69-71° (from cyclohexane-ethyl acetate), ν_{max} 2155 ($C=\overset{+}{N}=\overset{-}{N}$), 1725 and 1604 (C=O) and 1515 and 1334 (NO_2) cm^{-1}, δ_H ($CDCl_3$)

4.13 (2H, q, J = 7 Hz, CH_2), 3.90 (2H, q, J = 7 Hz, CH_2), 2.41 (3H, s, CH_3), 1.31 (3H, t, J = 7 Hz, CH_3) and 1.15 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave a tan solid (0.20g), m.p. >360°, from which no identifiable material could be obtained.

Ethyl 1-Ethyl-2-methylimidazo[3,4-d]isoxazole-6-carboxylate (138)

A solution of ethyl 2-diazo-3-(1-ethyl-2-methyl-4-nitroimidazol-5-yl)-3-oxopropanoate (137) (1.2g; 0.004mol) in anhydrous toluene (20.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 5h.

The mixture was rotary evaporated to give a brown gum (1.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) gave a multicomponent orange oil (0.13g) which was not further investigated.

Further elution with hexane-ethyl acetate (3:2) afforded ethyl 1-ethyl-2-methylimidazo[3,4-d]isoxazole-6-carboxylate (138) (0.53g; 60%) which formed colourless plates, m.p. 113-115° (lit.,[58] 113-114°), ν_{max} 1728 (C=O) cm^{-1}, δ_H ($CDCl_3$) 4.43 (2H, q, J = 7 Hz, CH_2), 4.18 (2H, q, J = 7 Hz, CH_2), 2.53 (3H, s, CH_3), 1.41 (3H, t, J = 7 Hz, CH_3) and 1.36 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

Dialkyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioates (139a) and (139b)

A solution of the corresponding dialkyl 2-(3-nitropyrid-2-yl)propanedioate (0.01mol) in glacial acetic acid (50.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (25.0ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 24h then worked up as described for the individual reactions below.

(i) Dimethyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioate (139a)

The mixture from dimethyl 2-(3-nitropyrid-2-yl)propanedioate (102b) was concentrated by rotary evaporation to one half of its original volume then diluted with water (30.0ml) and the resulting solution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 50.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (25.0ml) and rotary evaporated to afford dimethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (139a) (1.9g; 70%) which formed pale yellow prisms, m.p. 110-112° (from toluene), ν_{max} 3440 (OH), 1767 and 1740 (C=O) and 1536 and 1362 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.70 (1H, dd, J = 5 and 2 Hz, ArH), 8.29 (1H, dd, J = 8 and 2 Hz, ArH), 7.53 (1H, dd, J = 8 and 5 Hz, ArH), 4.84 (1H, bs, OH) (exch.) and 3.85 (6H, s, 2 x CH_3).

(ii) Di-*tert*-butyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioate (139b)

The mixture from di-*tert*-butyl 2-(3-nitropyrid-2-yl)propanedioate (102c) was concentrated by rotary evaporation to one half of its original volume then diluted with water (30.0ml) and the resulting solution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 50.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (25.0ml) and rotary evaporated to give a yellow oil. This was triturated with hexane to afford di-*tert*-butyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (139b) (15%) which formed pale yellow, irregular crystals, m.p. 113-115° (from hexane-toluene), ν_{max} 3454 (OH), 1725 (C=O) and 1532 and 1369 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.768 (1H, dd, J = 5 and 2 Hz, ArH), 8.27 (1H, dd, J = 8 and 2 Hz, ArH), 7.46 (1H, dd, J = 8 and 5 Hz, ArH), 4.60 (1H, bs, OH) (exch.) and 1.49 (18H, s, 6 x CH_3).

Rotary evaporation of the hexane mother liquor gave only a negligible amount of material.

Diethyl 2-Methyl-2-(3-nitropyrid-2-yl)propanedioate (146)

A stirred suspension of sodium hydride (0.26g; 0.011mol) in anhydrous dimethylformamide (10.0ml) was treated dropwise with a solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (2.8g; 0.01mol) in anhydrous dimethylformamide (20.0ml). and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15 min. The mixture was then was treated dropwise with a solution of methyl iodide (5.7g; 0.04mol) in anhydrous dimethylformamide (10.0ml) and the resulting solution stirred at room temperature with exclusion of atmospheric moisture for 24h.

The mixture was diluted with water (5.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (40.0ml). Extraction of the mixture with methylene chloride (3 x 50.0ml) gave a red oil (3.3g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (4:1) afforded diethyl 2-methyl-2-(3-nitropyrid-2-yl)propanedioate (146) (2.4g; 81%) which formed colourless, irregular crystals, m.p. 55-56° (from cyclohexane), ν_{max} 1755 and 1737 (C=O) and 1539 and 1363 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.69 (1H, dd, J = 5 and 2 Hz, ArH), 8.30 (1H, dd, J = 8 and 2 Hz, ArH), 7.44 (1H, dd, J = 8 and 5 Hz, ArH), 4.16 (2H, q, J = 7 Hz, CH_2), 4.15 (2H, q, J = 7 Hz, CH_2), 1.96 (3H, s, CH_3) and 1.16 (6H, t, J = 7 Hz, 2 x CH_3), δ_C ($CDCl_3$) 168.6 (quat), 153.4 (quat), 151.7 (CH), 145.0 (quat), 133.4 (CH), 123.1 (CH), 62.7 (quat), 61.8 (CH_2), 21.4 (CH_3) and 13.5 (CH_3).

Final elution with methanol gave a red oil whose i.r. spectrum indicated that it was mainly dimethylformamide and so was not further investigated.

The Attempted Oxidation of Diethyl 2-(3-Nitropyrid-2-yl)propanedioate (102a)

A solution of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.4g; 0.005mol) in anhydrous acetonitrile (25.0ml) was treated with activated manganese

dioxide (2.5g) and the resulting suspension was stirred at room temperature under a nitrogen atmosphere for 48h.

The mixture was filtered through celite and rotary evaporated to give only unreacted diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (1.2g; 88%) as a yellow solid, m.p. 59-61°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Oxidation of Diethyl 2-(5-Nitropyrid-2-yl)propanedioate (121) using Hydrogen Peroxide in Acetic Acid

A solution of diethyl 2-(5-nitropyrid-2-yl)propanedioate (121) (1.4g; 0.005mol) in glacial acetic acid (25.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (12.5ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 20h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (15.0ml) and the resulting soution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 50.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (10.0ml) and rotary evaporated to give an orange oil (1.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded diethyl 2-hydroxy-2-(5-nitropyrid-2-yl)propanedioate (149) (0.89g; 60%) as a colourless oil, b.p. 124-128°/ 0.05mmHg, ν_{max} 3456 (OH), 1742 (C=O) and 1529 and 1357 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.34 (1H, dd, J = 3 and 1 Hz, ArH), 8.53 (1H, dd, J = 10 and 3 Hz, ArH), 7.94 (1H, dd, J = 10 and 1 Hz, ArH), 5.37 (1H, bs, OH) (exch.) and 4.30 (4H, q, J = 7 Hz, 2 x CH_2), and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

Elution with hexane-ethyl acetate (7:3) afforded diethyl 2-hydroxy-2-(5-nitropyrid-2-yl)propanedioate *N*-oxide (150) (0.13g; 8%) which formed colourless needles, m.p. 106-107°, (from hexane-ethanol), ν_{max} 3355 (OH), 1770 and 1740 (C=O) and 1539 and 1358 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.01 (1H, dd, J = 2 and 1 Hz,

ArH), 8.09 (1H, dd, J = 9 and 2 Hz, ArH), 7.72 (1H, d, J = 9 Hz, ArH), 5.92 (1H, bs, OH) (exch.) and 4.35 (4H, q, J = 7 Hz, 2 x CH_2), and 1.31 (6H, t, J = 7 Hz, 2 x CH_3).

Final elution with methanol gave no further material.

Oxidations Reactions of Diethyl 2-(3-Nitropyrid-4-yl)propanedioate (111)

(i) Diethyl 2-Hydroxy-2-(3-nitropyrid-4-yl)propanedioate *N*-oxide (151)

A solution of diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (1.4g; 0.005mol) in glacial acetic acid (25.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (12.5ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 24h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (15.0ml) and the resulting solution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 50.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (10.0ml) and rotary evaporated to afford diethyl 2-hydroxy-2-(3-nitropyrid-4-yl)propanedioate *N*-oxide (151) (0.30g; 19%) which formed colourless plates, m.p. 161-163°, (from ethanol), ν_{max} 3118 (OH), 1761 and 1736 (C=O) and 1557 and 1366 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.66 (1H, d, J = 2 Hz, ArH), 8.30 (1H, dd, J = 7 and 2 Hz, ArH), 7.71 (1H, d, J = 7 Hz, ArH), 4.80 (1H, bs, OH) (exch.), 4.32 (2H, q, J = 7 Hz, CH_2), 4.31 (2H, q, J = 7 Hz, CH_2), and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

(ii) Diethyl 2-Hydroxy-2-(3-nitropyrid-4-yl)propanedioate (152)

A solution of diethyl 2-(3-nitropyrid-4-yl)propanedioate (111) (1.4g; 0.005mol) in anhydrous acetonitrile (25.0ml) was treated with activated manganese dioxide (2.5g) and the resulting suspension was stirred at room temperature for 72h.

The mixture was filtered through celite and the filtrate was rotary evaporated to give an orange gum which was triturated with diethyl ether to afford diethyl 2-hydroxy-2-(3-nitropyrid-4-yl)propanedioate (152) (0.40g; 27%) which formed colourless needles, m.p. 139-140°, (from ethanol), ν_{max} 3350-2250 br (OH), 1756 and 1741 (C=O) and 1537 and 1363 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.10 (1H, s, ArH), 8.82 (1H, d, J = 5 Hz, ArH), 7.67 (1H, d, J = 5 Hz, ArH), 4.35 (2H, q, J = 7 Hz, CH_2), 4.31 (2H, q, J = 7 Hz, CH_2), and 1.28 (6H, t, J = 7 Hz, 2 x CH_3).

Rotary evaporation of the ethereal mother liquor gave an orange gum (0.43g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a six component mixture which was therefore not further investigated.

Attempted Hydrolysis Reactions of Diethyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128)

(a) A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.30g; 0.001mol) in 2M aqueous sodium hydroxide (5.0ml) was stirred and heated under reflux for 1h.

Acidification of the mixture with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 25.0ml) gave no material.

Neutralisation of the mixture by addition of solid sodium acetate followed by extraction with methylene chloride (3 x 25.0ml) gave no material.

Subjection of the aqueous mixture to cation-exchange chromatography over Amberlite IR-120 resin gave only an intractable brown glass (0.71g).

(b) A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.60g; 0.002mol) in 2M aqueous hydrochloric acid (10.0ml) was stirred and heated under reflux for 1h.

Rotary evaporation of the mixture gave an intractable, black solid (0.38g) from which no identifiable material could be obtained.

(c) A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (1.2g; 0.004mol) in 2M aqueous sodium hydroxide (10.0ml) was stirred and heated at 50° (oil bath) for 0.5h.

Acidification of the mixture with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 10.0ml) gave only a negligible amount of material.

Subjection of the aqueous mixture to cation-exchange chromatography over Amberlite IR-120 resin gave only an intractable brown glass (0.13g).

(d) A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.60g; 0.002mol) in 50% w/v aqueous sulphuric acid (1.5ml) was stirred and heated at 120° (oil bath) for 8h.

The mixture was diluted with water (20.0ml) and basified with solid sodium hydrogen carbonate then extracted with methylene chloride (3 x 20.0ml) to give only a negligible amount of material.

Attempted Oxidation Reactions of Diethyl 2-Hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128)

(a) A stirred solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.60g; 0.002mol) in glacial acetic acid (7.0ml) and water (3.0ml) was treated portionwise with chromium trioxide (1.2g) and the resulting purple mixture was stirred and heated at 100° (oil bath) for 0.5h.

The mixture was rotary evaporated and the residue was treated with water (5.0ml) and filtered to give only an intractable, multicomponent, brown solid (0.26g), m.p. >360°, which was not further investigated.

Extraction of the aqueous mother liquor with methylene chloride (3 x 10.0ml) gave only a negligible amount (0.08g) of unidentifiable material.

(b) A solution of diethyl 2-hydroxy-2-(3-nitropyrid-2-yl)propanedioate (128) (0.60g; 0.002mol) in 2M aqueous sodium hydroxide (5.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (5.0ml) and the mixture was stirred at room temperature for 24h.

Neutralisation of the mixture by addition of 2M aqueous hydrochloric acid then solid sodium acetate followed by extraction with methylene chloride (3 x 25.0ml) gave no material.

Ethyl 2-(3-Nitropyrid-2-yl)ethanoate *N*-Oxide (158)

A solution of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (1.1g: 0.005mol) in glacial acetic acid (25.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (12.5ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 24h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (50.0ml) and the resulting soution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 50.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (50.0ml) and rotary evaporated to give an yellow oil (0.30g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:4) afforded ethyl 2-(3-nitropyrid-2-yl)ethanoate *N*-oxide (158) as a yellow oil, b.p 130-140°/ 0.01mmHg, ν_{max} 1732 (C=O) and 1537 and 1349 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.45 (1H, dd, J = 7 and 1 Hz,

ArH), 7.84 (1H, dd, J = 9 and 1 Hz, ArH), 7.35 (1H, dd, J = 9 and 7 Hz, ArH), 4.36 (2H, s, CH_2) and 4.17 (2H, q, J = 7 Hz, CH_2), and 1.23 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave a multicomponent yellow oil (0.06g) which was not further investigated.

Reactions of Ethyl 2-(3-Nitropyrid-2-yl)ethanoate (104a) with Isoamyl Nitrite

(a) A stirred suspension of sodium hydride (0.096g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was cooled to 0° (ice-salt bath) then treated dropwise with a solution of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.42g; 0.002mol) in anhydrous 1,2-dimethoxyethane (5.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min and then was treated dropwise with a solution of isoamyl nitrite (0.23g; 0.002mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the resulting solution stirred and heated at 50° (oil bath) with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated and the residue treated with water (5.0ml). The resulting solution was acidified with glacial acetic acid and extracted with methylene chloride (3 x 10.0ml) to give a brown oil (0.70g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded 2-methyl-3-nitropyridine (161) (0.21g; 76%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample prepared before.

Elution with hexane-ethyl acetate (7:3) gave an unidentified brown solid (0.072g), m.p. 168-173°, ν_{max} 2237 (CN) and 1524 and 1327 (NO_2) cm^{-1}, which was not further investigated.

Final elution with methanol gave only a negligible amount of material.

(b) A stirred solution of sodium (0.046g; 0.002g.atom) in anhydrous ethanol (2.0ml) was treated with isoamyl nitrite (0.23g; 0.002mol) then a solution of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.42g; 0.002mol) in anhydrous ethanol (8.0ml) was added dropwise and the resulting mixture stirred at room temperature with exclusion of atmospheric moisture for 19h.

The mixture was rotary evaporated and the residue was treated with water (5.0ml). The resulting solution was acidified with glacial acetic acid and extracted with methylene chloride (3 x 10.0ml) to give a brown oil (0.33g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded 2-methyl-3-nitropyridine (161) (0.16g; 58%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Elution with hexane-ethyl acetate (4:1) gave a two component orange gum (0.046g) which was not further investigated.

Further elution with hexane-ethyl acetate (9:1) afforded ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate 2-oxime (160) (0.093g; 19%) which formed colourless, irregular crystals ,m.p. 125-127° (from toluene), ν_{max} 3154 (OH), 1721 (C=O) and 1538 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.94 (1H, dd, J = 5 and 2 Hz, ArH), 8.51 (1H, dd, J = 8 and 2 Hz, ArH), 7.59 (1H, dd, J = 8 and 5 Hz, ArH), 7.0-5.7 (1H, bs, OH) (exch.), 4.32 (2H, q, J = 7 Hz, CH_2), and 1.27 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a negligible amount of material.

The Reaction of Ethyl 2-(3-Nitropyrid-2-yl)ethanoate (104a) with Ethyl Nitrite

A stirred solution of sodium (0.046g; 0.002g.atom) in anhydrous ethanol (2.5ml) was treated with a solution of ethyl 2-(3-nitropyrid-2-yl)ethanoate (104a) (0.42g; 0.002mol) in anhydrous ethanol (7.5ml). The mixture was cooled to 0° (ice-salt bath) then treated dropwise with a 15% w/v solution of ethyl nitrite in ethanol

(1.1ml; 0.002mol ethyl nitrite) and the resulting mixture stirred at room temperature with exclusion of atmospheric moisture for 18h.

The mixture was rotary evaporated and the residue treated with water (5.0ml). The resulting solution was neutralised by the addition of 2M aqueous hydrochloric acid followed by solid sodium acetate and extracted with methylene chloride (3 x 10.0ml) to give a red gum (0.28g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded 2-methyl-3-nitropyridine (161) (0.21g; 76%) as a orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Elution with hexane-ethyl acetate (7:3) gave a tan solid (0.03g), m.p. 183-187° (decomp.) which was not further investigated.

Further elution with hexane-ethyl acetate (7:3) afforded ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate 2-oxime (160) (0.10g; 21%) as a cream solid, m.p. 120-122° identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Final elution with methanol gave only a negligible amount (0.06g) of an intractable black gum.

2-Methyl-3-nitropyridine (161)

2-Methyl-3-nitropyridine (161) was prepared by the hydrolysis of diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) in 50% w/v aqueous sulphuric acid as described by Liu, Liu and Sartorelli[43] as a yellow solid (yield 89%), m.p. 33-34° (lit.,[43] 28-30°), ν_{max} 1566 and 1345 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.71 (1H, dd, J = 5 and 2 Hz, ArH), 8.25 (1H, dd, J = 8 and 2 Hz, ArH), 7.32 (1H, dd, J = 8 and 5 Hz, ArH), 2.85 (3H, s, CH_3).

Found: m/z (EIMS), 138 (M^+).

Calc. for $C_6H_6N_2O_2$: M, 138.

Ethyl 2-(3-Nitropyrid-2-yl)-2-oxoethanoate (162)

A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (2.4g; 0.01mol) in glacial acetic acid (50.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (25.0ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 24h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (100ml) and the resulting solution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 100ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (50.0ml) and rotary evaporated to afford ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate (162) (1.1g, 49%) which formed colourless, irregular crystals, m.p. 69-70° (from ethanol), ν_{max} 1754 and 1729 (C=O) and 1538 and 1354 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.95 (1H, dd, J = 5 and 1 Hz, ArH), 8.49 (1H, dd, J = 8 and 1 Hz, ArH), 7.67 (1H, dd, J = 8 and 5 Hz, ArH) 4.36 (2H, q, J = 7 Hz, CH_2), and 1.34 (3H, t, J = 7 Hz, CH_3).

Attempted Oxidation Reactions of Ethyl 2-Cyano-2-(3-nitropyrid-2-yl)ethanoate (105d)

(a) A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (0.94g; 0.004mol) in 1M aqueous sodium hydroxide (10.0ml) was treated with 30%w/w aqueous hydrogen peroxide solution (2.0ml) and the resulting solution was stirred at room temperature for 2h.

The mixture was acidified with 2M aqueous hydrochloric acid and was extracted with methylene chloride (3 x 50.0ml) to give a multicomponent tan solid (0.054g), m.p. 104-106°, which was not further investigated.

(b) A solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (1.2g; 0.005mol) in anhydrous acetonitrile (25.0ml) was treated with activated manganese dioxide (2.5g) and the resulting suspension was stirred at room temperature with exclusion of atmospheric moisture for 24h.

The mixture was filtered through celite and rotary evaporated to afford unreacted ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (1.0g; 83%) as an orange solid, m.p. 133-136°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Ethyl 2-Cyano-2-(3-nitropyrid-2-yl)propanoate (164)

A stirred suspension of sodium hydride (0.13g; 0.0055mol) in anhydrous dimethylformamide (6.25ml) was treated dropwise with a solution of ethyl 2-cyano-2-(3-nitropyrid-2-yl)ethanoate (105d) (1.2g; 0.005mol) in anhydrous dimethylformamide (12.5ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15 min. The mixture was treated dropwise with a solution of methyl iodide (2.8g; 0.02mol) in anhydrous dimethylformamide (6.25ml) and the resulting solution was stirred at room temperature with exclusion of atmospheric moisture for 23h.

The mixture was diluted with water (2.5ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (25.0ml). Extraction of the mixture with methylene chloride (3 x 50.0ml) gave a brown oil (1.8g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (7:3) afforded a yellow oil which was purified by kugelrohr distillation to give ethyl 2-cyano-2-(3-nitropyrid-2-yl)propanoate (164) (1.1g; 92%) as a yellow, crystalline solid, m.p. 46-47° ,b.p. 114-129°/ 1.0mmHg, ν_{max} 2249 (CN), 1746 (C=O) and 1570 and 1335 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.88 (1H, dd, J = 5 and 2 Hz, ArH), 8.50 (1H, dd, J = 8 and 2 Hz, ArH), 7.63 (1H, dd, J = 8 and 5 Hz, ArH), 4.30 (2H, q, J = 7 Hz, CH_2), 2.18 (3H, s, CH_3) and 1.31 (3H, t,

J = 7 Hz, CH_3), δ_C ($CDCl_3$) 167.1 (quat), 152.6 (CH), 147.9 (quat), 144.2 (quat), 134.0 (CH), 124.8 (CH), 117.4 (quat), 63.4 (CH_2), 49.7 (quat), 23.3 (CH_3) and 13.7 (CH_3).

Final elution with methanol gave a small amount of a brown oil (0.04g) which was not further investigated.

Attempted Hydrolysis Reactions of Ethyl 2-(3-Nitropyrid-2-yl)-2-oxoethanoate (162)

(a) A solution of ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate (162) (0.45g; 0.002mol) in 2M aqueous sodium hydroxide (5.0ml) was stirred and heated under reflux for 1h.

Acidification of the mixture with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 10.0ml) gave a multicomponent, gummy, orange solid (0.05g) which was not further investigated.

Neutralisation of the aqueous phase by addition of solid sodium acetate followed by extraction with methylene chloride (3 x 10.0ml) gave no material.

(b) A solution of ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate (162) (0.45g; 0.002mol) in ethanol (7.5ml) and 2M aqueous hydrochloric acid (2.5ml) was stirred and heated under reflux for 1h.

Rotary evaporation of the mixture gave only unreacted ethyl 2-(3-nitropyrid-2-yl)-2-oxoethanoate (162) (0.41g; 91%) as a brown solid, m.p. 60-65°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

2-Cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171)

A stirred suspension of sodium hydride (10.6g; 0.44mol) in anhydrous dimethylformamide (200ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of malononitrile (29.0g; 0.44mol) in anhydrous dimethylformamide

(100ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min and then was treated dropwise with a solution of 2-chloro-3-nitropyridine (101) (31.7g; 0.2mol) in anhydrous dimethylformamide (100ml) and the resulting solution stirred at room temperature with exclusion of atmospheric moisture for 2h.

The mixture was diluted with water (50.0ml), stirred at room temperature for 10min then rotary evaporated and the residue treated with water (300ml). The resulting mixture was acidified with concentrated hydrochloric acid and the precipitated solid collected to afford 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (37.4g; 99%) as an orange solid, m.p. 178-180° (decomp.), which was purified by dissolution in warm 2M aqueous sodium hydroxide and reprecipitation with 2M aqueous hydrochloric acid to give an orange powder, m.p. 182-184° (decomp.), ν_{max} 2221 and 2160 (CN), 1630 (C=C) and 1532 and 1353 (NO_2) cm^{-1}, δ_H [$(CD_3)_2S$=O] 10.2 (1H, bs, NH) (exch.), 8.35 (1H, dd, J = 8 and 2 Hz, ArH), 8.15 (1H, dd, J = 6 and 2 Hz, ArH), and 6.88 (1H, dd, J = 8 and 6 Hz, ArH), δ_C [$(CD_3)_2S$=O] 148.2 (quat), 144.7 (CH), 139.24 (quat), 139.16 (CH), 116.9 (2 x quat), 112.4 (CH) and 40.7 (quat).

Extraction of the aqueous mother liquor with methylene chloride (3 x 150ml) gave a red oil (17.0g) which was not further investigated.

2-Cyano-2-(3-nitropyrid-2-yl)propanenitrile (172)

A stirred suspension of sodium hydride (0.26g; 0.011mol) in anhydrous dimethylformamide (10.0ml) was treated dropwise with a solution of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (1.9g; 0.01mol) in anhydrous dimethylformamide (20.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min. The mixture was treated dropwise with a solution of methyl iodide (5.7g; 0.04mol) in anhydrous dimethylformamide

(10.0ml) and the resulting solution was stirred at room temperature with exclusion of atmospheric moisture for 19h.

The mixture was diluted with water (5.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (40.0ml). Extraction of the mixture with methylene chloride (3 x 50.0ml) gave a red oil (3.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded an orange oil which was purified by kugelrohr distillation to give 2-cyano-2-(3-nitropyrid-2-yl)propanenitrile (172) (0.91g; 46%) as yellow crystals, m.p. 54-56°, b.p. 160-170°/ 2.0mmHg, ν_{max} 1536 and 1358 (NO_2) cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.90 (1H, dd, J = 5 and 2 Hz, ArH), 8.49 (1H, dd, J = 8 and 2 Hz, ArH), 7.74 (1H, dd, J = 8 and 5 Hz, ArH) and 2.46 (3H, s, CH_3), δ_C[$(CD_3)_2S$=O] 152.9 (CH), 144.3 (quat), 143.3 (quat), 134.7 (CH), 126.3 (CH), 113.5 (2 x quat), 37.7 (quat) and 25.2 (CH_3).

Final elution with methanol gave a brown oil (1.3g) which was not further investigated.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and collection of the precipitated solid gave unreacted 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (0.78g; 41%) as an orange solid, m.p. 178° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Oxidation Reactions of 2-Cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171)

(a) A solution of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (15.0g; 0.08mol) in glacial acetic acid (200ml) was treated with 30% w/v aqueous hydrogen peroxide solution (100ml) and the resulting mixture was stirred and heated at 50° (oil bath) for 18h.

The mixture was concentrated by rotary evaporation to one third of its original volume then diluted with water (100ml) and the resulting solution basified with 10%

w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 250ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (100ml) and rotary evaporated to give a waxy, orange solid which was washed with diethyl ether to afford 3-nitropyridine-1-*N*-oxide (174) (4.4g; 39%) which formed yellow, irregular crystals, m.p. 172-173° (from water) (lit.,[76] 172-173°), ν_{max} 1523 and 1360 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2S{=}O]$ 8.94 (1H, dd, J = 4 and 2 Hz, ArH), 8.58 (1H, ddd, J = 6, 2 and 1 Hz, ArH), 8.10 (1H, dd J = 9, 2 and 1 Hz, ArH) and 7.66 (1H, dd, J = 9 and 6 Hz, ArH).

Rotary evaporation of the ethereal mother liquor gave only a multicomponent orange oil (0.30g) which was not further investigated.

(b) A solution of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (15.0g; 0.08mol) in 1M aqueous sodium hydroxide (200ml) was treated with 30% w/v aqueous hydrogen peroxide solution (40.0ml) and the mixture was stirred for 3h during which time the reaction temperature rose to 60° and gas was evolved.

The mixture was acidified with 2M aqueous hydrochloric acid and was continuously extracted with methylene chloride for 72h to give a yellow solid (2.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded 3-nitropyridine (175) (1.6g; 16%) as a cream solid, m.p. 40-41° (lit.,[77] 40°), ν_{max} 1516 and 1351 (NO_2) cm^{-1}.

Found: m/z (EIMS), 124 (M^+).

Calc. for $C_5H_4N_2O_2$: M, 124.

Elution with hexane-ethyl acetate (4:1) afforded 3-nitropyridine-2-carboxamide (176) (0.19g; 1.4%) which formed yellow, irregular crystals, m.p. 213-214° (lit.,[73] 211°), ν_{max} 3435, 3287 and 3177 (NH), 1680 (C=O) and 1535 and 1370 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2S{=}O]$ 8.85 (1H, dd, J = 5 and 1 Hz, ArH), 8.55 (1H, bs, NH) (exch.), 8.44 (1H, dd, J = 8 and 1 Hz, ArH), 7.85 (1H, bs, NH) (exch.) and 7.81 (1H, dd, J = 8 and 5 Hz, ArH).

Final elution with methanol gave no further material.

The Attempted Oxidation of 2-Cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) Using Hydrogen Peroxide in Aqueous Alkali at Low Temperature

A solution of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (1.9g; 0.01mol) in 1M aqueous sodium hydroxide (25.0ml) was cooled to 5° (ice bath) and treated with stirring with 30% w/v aqueous hydrogen peroxide solution (5.0ml) and the mixture stirred at 5° (ice bath) for 2h.

The mixture was acidified with concentrated hydrochloric acid and the suspended solid was collected to give only unreacted 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (1.3g; 68%) as an orange solid, m.p. 181° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride (3 x 50.0ml) gave no further material.

3-Nitropyridine-2-carboxylic Acid (156)

A solution of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile (171) (18.8g; 0.1mol) in 1M aqueous sodium hydroxide (250ml) was cooled to 5° (ice-water bath) and treated with stirring with 30% w/v aqueous hydrogen peroxide solution (50.0ml) and the mixture stirred at room temperature for 2h. The reaction temperature rose to 40° after 1h and was kept at this temperature by the application of an ice-water cooling bath when necessary.

The mixture was acidified with concentrated hydrochloric acid and the suspended solid collected to afford 3-nitropyridine-2-carboxylic acid (156) (12.2g; 73%) which formed cream, irregular crystals, m.p. 123-124° (decomp.) (lit.,[71] 120-121°), ν_{max} 3000-1883 br (OH), 1708 (C=O) and 1535 and 1358 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2S{=}O]$ 8.93 (1H, dd, J = 5 and 1 Hz, ArH), 8.58 (1H, dd, J = 8 and 1 Hz, ArH), and 7.84 (1H, dd, J = 8 and 5 Hz, ArH).

Extraction of the aqueous mother liquor with methylene chloride (3 x 250ml) gave no further material.

3-Nitropyridine-2-carboxylic Acid Chloride (133)

A mixture of 3-nitropyridine-2-carboxylic acid (156) (0.84g; 0.005mol) and thionyl chloride (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The resulting mixture was rotary evaporated and the residue azeotroped with anhydrous toluene (5.0ml) to give 3-nitropyridine-2-carboxylic acid chloride (133) (0.93g; 100%) as a brown oil, ν_{max} 1811 and 1772 (C=O) and 1536 and 1354 (NO_2) cm^{-1}, which was used without further purification.

Ethyl 3-Nitropyridine-2-carboxylate (177)

A solution of 3-nitropyridine-2-carboxylic acid chloride (133) (0.35g; 0.0018mol) in anhydrous ethanol (5.0ml) was stirred at room temperature with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated to give a brown gum (0.34g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 3-nitropyridine-2-carboxylate (177) (0.33g; 95%) as a colourless oil, b.p. 120-125°/ 1.0mmHg, ν_{max} 1744 (C=O) and 1535 and 1353 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 8.81 (1H, dd, J = 5 and 2 Hz, ArH), 8.32 (1H, dd, J = 8 and 2 Hz, ArH), 7.58 (1H, dd, J = 8 and 5 Hz, ArH), 4.42 (2H, q, J = 7Hz, CH_2) and 1.34 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a negligible amount of material.

2-Cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178)

A stirred suspension of sodium hydride (0.53g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of malononitrile (1.5g; 0.022mol) in anhydrous dimethylformamide (5.0ml). The resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min, then treated dropwise with a solution of 4-chloro-3-nitropyridine (110) (1.6g; 0.01mol) in anhydrous dimethylformamide (5.0ml) and the resulting solution stirred at room temperature with exclusion of atmospheric moisture for 2h.

The mixture was diluted with water (2.5ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (25.0ml). The resulting mixture was acidified with concentrated hydrochloric acid and the precipitated solid collected to afford 2-cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178) (1.1g; 59%) which formed brown, irregular crystals, m.p. 278-280° (decomp.) (from glacial acetic acid-dimethylformamide), ν_{max} 3222 (NH), 2210 and 2183 (CN), 1643 (C=C) and 1566 and 1327 (NO_2) cm^{-1}, δ_H [$(CD_3)_2S$=O] 8.83 (1H, s, ArH), 7.90 (1H, d, J = 7 Hz, ArH) and 7.14 (1H, d, J = 7 Hz, ArH), δ_C [$(CD_3)_2S$=O] 146.7 (quat), 139.2 (CH), 136.6 (CH), 135.9 (quat), 118.0 (quat), 117.4 (CH), 115.8 (quat) and 88.8 (quat).

Extraction of the aqueous mother liquor with methylene chloride (3 x 25.0ml) gave a black oil (1.0g) which was not further investigated.

Attempted Oxidation Reactions of 2-Cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178)

A solution of 2-cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178) (0.56g; 0.003mol) in 1M aqueous sodium hydroxide (7.5ml) was treated with 30% w/v aqueous hydrogen peroxide solution (1.5ml) and the mixture was stirred at the appropriate temperature for 6h then worked up as described for the individual reactions below.

(i) The mixture from the reaction at room temperature was acidified with concentrated hydrochloric acid and the precipitated solid collected to give only unreacted 2-cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178) (0.39g; 72%) as a yellow solid, m.p. 276-278° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride (3 x 20.0ml) gave no further material.

(ii) The mixture from the reaction at 40° (oil bath) was acidified with concentrated hydrochloric acid and the precipitated solid collected to give only unreacted 2-cyano-2-(3-nitropyrid-4-yl)ethanenitrile (178) (74%) as a yellow solid, m.p. 277-280° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride gave no further material.

3-Nitropyridine-2-carboxamides (180a-c)

A stirred suspension of fused sodium acetate (4.1g; 0.05mol) in glacial acetic acid (12.5ml) was treated with the corresponding amine (0.01mol) then dropwise with a solution of 3-nitropyridine-2-carboxylic acid chloride (133) (1.9g; 0.01mol) in glacial acetic acid (12.5ml) and the resulting suspension was stirred at room temperature with exclusion of moisture for 3h then worked up as described for the individual reactions below.

(i) 3-Nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a)

The mixture from 2-(*N*-methylamino)acetonitrile hydrochloride was rotary evaporated and the residue was treated with water (25.0ml) and extracted with

methylene chloride to afford 3-nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) (70%) which formed tan needles, m.p. 145-147° (from methanol), ν_{max} 1662 (C=O) and 1531 and 1351 (NO_2) cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.97 (1H, dd, J = 5 and 1 Hz, ArH), 8.69 (1H, dd, J = 8 and 1 Hz, ArH), 7.84 (1H, dd, J = 8 and 5 Hz, ArH), 4.69 [(2H, s, CH_2), conformer A], 4.52 [(2H, s, CH_2), conformer B], 3.34 [(3H, s, CH_3), conformer B] and 2.92 [(3H, s, CH_3), conformer A].

Acidification of the aqueous phase with concentrated hydrochloric acid followed by extraction with methylene chloride gave no further material.

(ii) 3-Nitropyridine-2-(*N*-cyanomethyl-*N*-phenyl)carboxamide (180b)

The mixture from *N*-phenylaminoacetonitrile was rotary evaporated and the residue was treated with water (25.0ml) and extracted with methylene chloride (3 x 25.0ml) to give a brown gum which was triturated with methanol to give a solid, which was combined with a second crop obtained by rotary evaporation of the methanolic mother liquor and flash-chromatography of the residue in hexane-ethyl acetate (2:3) over silica, to afford 3-nitropyridine-2-(*N*-cyanomethyl-*N*-phenyl)carboxamide (180b) (total 1.4g; 50%) which formed colourless prisms, m.p. 138-140° (from methanol), ν_{max} 1682 (C=O) and 1531 and 1353 (NO_2) cm^{-1}, δ_H($CDCl_3$) 8.69 (1H, dd, J = 5 and 2 Hz, ArH), 8.25 (1H, dd, J = 8 and 2 Hz, ArH), 7.38 (1H, dd, J = 8 and 5 Hz, ArH), 7.30-7.19 (5H, m, 5 x ArH) and 4.84 (2H, s, CH_2).

(iii) 3-Nitropyridine-2-[*N*-(ethoxycarbonylmethyl)-*N*-methyl]carboxamide (180c)

The mixture from 2-(*N*-methylamino)ethanoate hydrochloride was rotary evaporated and the residue was treated with water (25.0ml) and extracted with methylene chloride to give a brown oil which was flash-chromatogrphed over silica.

Elution with hexane-ethyl acetate (1:1) afforded 3-nitropyridine-2-[*N*-(ethoxycarbonyl)methyl-*N*-methyl]carboxamide (180c) (88%) as a yellow oil b.p. 144-150°/ 0.1mmHg, ν_{max} 1746 and 1659 (C=O) and 1534 and 1352 (NO_2) cm^{-1},

$\delta_H(CDCl_3)$ (conformer A) 8.83 (1H, dd, J = 5 and 1 Hz, ArH), 8.42 (1H, dd, J = 8 and 1 Hz, ArH), 7.55 (1H, dd, J = 8 and 5 Hz, ArH), 4.29 (2H, s, CH_2), 4.21 (2H, q, J = 7 Hz, CH_2), 2.94 (3H, s, CH_3) and 1.27 (3H, t, J = 7 Hz, CH_3), (conformer B) 8.74 (1H, dd, J = 5 and 1 Hz, ArH), 8.37 (1H, dd, J = 8 and 1 Hz, ArH), 7.53 (1H, dd, J = 8 and 5 Hz, ArH), 4.13 (2H, q, J = 7 Hz, CH_2), 3.90 (2H, s, CH_2), 3.22 (3H, s, CH_3) and 1.20 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

1-Hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a)

(a) A solution of 3-nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) (0.88g; 0.004mol) in anhydrous ethanol (10.0ml) was treated with a solution of sodium (0.37g, 0.016g.atom) in anhydrous ethanol (10.0ml) and the resulting red mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 0.5h.

The mixture was rotary evaporated and the residue was treated with water (10.0ml) then the resulting solution extracted with methylene chloride (2 x 10.0ml) to give no material. Acidification of the aqueous phase with 2M aqueous hydrochloric acid and collection of the precipitated solid afforded 1-hydroxy-3-methylpyrido [3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.40g; 52%) which formed cream plates, m.p. 295-296° (decomp.) (from dimethylformamide), ν_{max} 3000-2000 br (OH) and 1713 and 1666 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 11.4 (1H, bs, OH) (exch.), 8.52 (1H, dd, J = 4 and 1 Hz, ArH), 7.93 (1H, dd, J = 9 and 1 Hz, ArH), 7.76 (1H, dd, J = 9 and 4 Hz, ArH) and 3.36 (3H, s, CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 25.0ml) gave only a small amount (0.06g) of an unidentified brown solid, m.p. 189-215° (decomp.).

Neutralisation of the aqueous phase by addition of solid sodium acetate followed by extraction with methylene chloride (3 x 25.0ml) gave no further material.

(b) A solution of 3-nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) (0.44g; 0.002mol) in anhydrous ethanol (10.0ml) was treated with a solution of powdered potassium hydroxide (0.56g, 0.01mol) in anhydrous ethanol (10.0ml) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue treated with water (10.0ml) and the resulting solution was extracted with methylene chloride (2 x 10.0ml) to give no material.

Acidification of the aqueous phase with 2M aqueous hydrochloric acid and collection of the precipitated solid afforded 1-hydroxy-3-methylpyrido [3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.10g; 26%) as a tan solid, m.p. 293-295° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Extraction of the aqueous mother liquor with methylene chloride (3 x 20.0ml) gave no further material.

(c) A stirred suspension of sodium hydride (0.19g; 0.008mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was treated dropwise with a solution of 3-nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) (0.44g; 0.002mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 3h.

The mixture was diluted with water (10.0ml), stirred at room temperature for 10 min then acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to afford 1-hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.12g; 31%) as a tan solid, m.p. 293-296° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared previously.

The Attempted Cyclisation of 3-Nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) Using Ethanolic Sodium Ethoxide at Room Temperature

A solution of 3-nitropyridine-2-(*N*-cyanomethyl-*N*-methyl)carboxamide (180a) (0.44g; 0.002mol) in anhydrous ethanol (5.0ml) was treated with a solution of sodium (0.18g, 0.008g.atom) in anhydrous ethanol (5.0ml) and the resulting red solution was stirred at room temperature with exclusion of atmospheric moisture for 0.5h.

The mixture was rotary evaporated, the residue treated with water (5.0ml) and the resulting solution was extracted with methylene chloride (2 x 5.0ml) to give no material.

Acidification of the aqueous phase with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 10.0ml) gave only a small amount (0.04g) of a multicomponent brown solid, m.p. 196-222° (decomp.), which was not further investigated.

1-Acetoxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (182)

(a) A mixture of 1-hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.39g; 0.002mol) and acetic anhydride (0.60ml) was heated at 100° (steam bath) with exclusion of atmospheric moisture for 45 min.

The resulting mixture was diluted with anhydrous diethyl ether (5.0ml) and the precipitated solid was collected to afford 1-acetoxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (182) (0.43g; 91%) which formed colourless irregular crystals, m.p. 215-216° (decomp.) (from glacial acetic acid), ν_{max} 1810, 1721 and 1675 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S{=}O]$ 8.63 (1H, dd, J = 4 and 1 Hz, ArH), 7.96 (1H, dd, J = 9 and 1 Hz, ArH), 7.80 (1H, dd, J = 9 and 4 Hz, ArH), 3.34 (3H, s, CH_3) and 2.50 (3H, s, CH_3).

Rotary evaporation of the ethereal mother liquor gave no further material.

(b) A solution of 1-hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.19g; 0.001mol) in acetic anhydride (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

The resulting mixture was rotary evaporated and the residue was washed with anhydrous diethyl ether to afford 1-acetoxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (182) 0.22g; 94%) as a tan solid, m.p. 214-216° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Rotary evaporation of the ethereal mother liquor gave no further material.

The Attempted Reduction of 1-Hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a)

A solution of 1-hydroxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181a) (0.19g; 0.001mol) in 2M aqueous sodium hydroxide (2.5ml) was stirred and heated under reflux then treated portionwise with sodium dithionite (0.38g) over 0.5h. The mixture was then stirred and heated under reflux for a further 0.5h.

Acidification of the aqueous phase with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 20.0ml) gave no material.

Neutralisation of the aqueous phase by addition of solid sodium acetate followed by extraction with methylene chloride (3 x 20.0ml) again gave no material.

The Reduction of 1-Acetoxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (182)

A solution of 1-acetoxy-3-methylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (182) (0.47g; 0.002mol) in dimethylformamide (10.0ml) was hydrogenated over 10% palladium-on-charcoal (0.05g) at room temperature and atmospheric pressure for 7h.

The mixture was filtered through celite and rotary evaporated to give a gummy solid which was washed with dimethylformamide (2.0ml) to give 3-methylpyrido

[3,2-d]pyrimidine-2,4(1H,3H)-dione (184) (0.065g; 19%) which formed tan, irregular crystals, m.p. >360° (from glacial acetic acid), ν_{max} 3100-2100 br (NH,OH) and 1730 and 1682 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 8.48 (1H, dd, J = 4 and 2 Hz, ArH), 7.68-7.56 (2H, m, 2 x ArH) and 3.26 (3H, s, CH_3).

Rotary evaporation of the organic mother liquor and crystallisation of the residue from glacial acetic acid gave unreacted 1-acetoxy-3-methylpyrido [3,2-d]pyrimidine-2,4(1H,3H)-dione (182) (0.075g; 16%), m.p. 210-213°, identified by comparison (m.p. and i.r. spectrum) to an authentic sample.

1-Hydroxy-3-phenylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181b)

(a) A solution of 3-nitropyridine-2-(*N*-cyanomethyl-*N*-phenyl)carboxamide (180b) (0.56g; 0.002mol) in anhydrous ethanol (5.0ml) was treated with a solution of sodium (0.18g, 0.008g.atom) in anhydrous ethanol (5.0ml) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 0.5h.

The mixture was rotary evaporated, the residue was treated with water (5.0ml) and the resulting solution was extracted with methylene chloride (2 x 10.0ml) to give no material

. Acidification of the aqueous phase with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 10.0ml) gave a brown gum which was triturated with ethyl acetate to afford 1-hydroxy-3-phenylpyrido[3,2-d]pyrimidine-2,4(1H,3H)-dione (181b) (0.13g; 26%) which formed brown, irregular crystals, m.p. 290-293° (from glacial acetic acid), ν_{max} 3383 and 3000-2000 br (OH) and 1739 and 1692 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 11.5 (1H, bs, OH) (exch.), 8.56 (1H, dd, J = 4 and 1 Hz, ArH), 7.99 (1H, dd, J = 8 and 1 Hz, ArH), 7.81 (1H, dd, J = 8 and 4 Hz, ArH) and 7.54-7.34 (5H, m, 5 x ArH).

Rotary evaporation of the organic mother liquor gave multicomponent brown oil (0.25g) which was not further investigated.

The Attempted Cyclisation of 3-Nitropyridine-2-[*N*-(ethoxycarbonylmethyl)-*N*-methyl]carboxamide (180c)

A solution of 3-nitropyridine-2-[*N*-(ethoxycarbonylmethyl)-*N*-methyl]carboxamide (180c) (0.53g; 0.002mol) in anhydrous ethanol (5.0ml) was treated with a solution of sodium (0.18g, 0.008g.atom) in anhydrous ethanol (5.0ml) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue was treated with water (10.0ml) and the resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (3 x 20.0ml) to give a brown gum (0.25g) whose t.l.c. in hexane-ethyl acetate (3:7) over silica showed it to be a complex, multicomponent mixture which was therefore not further investigated.

Ethyl 2-(3-Aminopyrid-2-yl)-2-hydroxyethanoate (187)

(a) A solution of ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (7.7g; 0.04mol) in ethyl acetate (200ml) was hydrogenated over 10% palladium-on-charcoal (0.80g) at room temperature and atmospheric pressure for 4h.

The mixture was filtered through celite and rotary evaporated to afford ethyl 2-(3-aminopyrid-2-yl)-2-hydroxyethanoate (187) (7.9g; 100%) which formed colourless, irregular crystals, m.p. 82-83° (from hexane-ethyl acetate), ν_{max} 3420, 3358 and 3265 (NH), 3158 (OH), 1734 (C=O) and 1660 (NH def.) cm^{-1}, δ_H ($CDCl_3$) 7.99 (1H, dd, J = 4 and 2 Hz, ArH), 7.07-7.01 (2H, m, 2 x ArH), 5.29 (1H, s, CH), 4.23 (2H, q, J = 7 Hz, CH_2) and 1.26 (3H, t, J = 7 Hz, CH_3).

(b) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.97g; 0.005mol) in ethyl acetate (25.0ml) was hydrogenated over 10% w/w palladium-on-charcoal (0.10g) at room temperature and atmospheric pressure for 0.5h.

The mixture was filtered through celite and rotary evaporated to afford ethyl 2-(3-aminopyrid-2-yl)-2-hydroxyethanoate (187) (0.84g; 86%) as an orange solid, m.p. 80-82°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Ethyl 2-Acetoxy-2-[3-(*N*,*N*-diacetylamino)pyrid-2-yl]ethanoate (190)

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-hydroxyethanoate (187) (0.20g; 0.001mol) in acetic anhydride (2.5ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

Rotary evaporation of the mixture gave a brown gum (0.37g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 2-acetoxy-2-[3-(*N*,*N*-diacetylamino)pyrid-2-yl]ethanoate (190) (0.20g; 63%) which formed colourless, plates, m.p. 124-125° (from hexane-toluene), ν_{max} 1760-1740 and 1730-1700 br (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.69 (1H, dd, J = 4 and 2 Hz, ArH), 7.51-7.44 (2H, m, 2 x ArH), 6.19 (1H, s, CH), 4.22 (2H, q, J = 7 Hz, CH_2), 2.33 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.12 (3H, s, CH_3) and 1.21 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (3:2) and then finally with methanol gave only a multicomponent orange gum (0.08g) which was not further investigated.

Attempted Reduction Reactions of Ethyl Isoxazolo[4,3-b]pyridine-3-carboxylate (103a)

(a) A solution of ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.38g; 0.002mol) in ethanol (14.0ml) and water (6.0ml) was treated with sodium dithionite (0.38g) and the mixture was stirred and heated under reflux for 1h. A second portion

of sodium dithionite (0.38g) was then added and the mixture was stirred and heated under reflux for a further 1h.

The mixture was rotary evaporated, the residuewas treated with water and the resulting solution was extracted with methylene chloride (3 x 10.0ml) to give only unreacted ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.08g; 21%) as a brown oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Rotary evaporation of the aqueous phase and extraction of the residue with boiling ethyl acetate (3 x 50.0ml) gave only an intractable orange solid (0.53g), m.p. 300° (decomp.), whose i.r. spectrum suggested that it was inorganic material.

(b) A stirred solution of ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.77g; 0.004mol) in tetrahydrofuran (20.0ml) was treated dropwise with 15% w/v aqueous titanium trichloride solution (2.0ml) and the mixture was stirred at room temperature under a nitrogen atmosphere for 0.5h.

The mixture was rotary evaporated, the residue was treated with 10% w/v aqueous sodium hydrogen carbonate solution (50.0ml) and the precipitated titanium dioxide was removed by filtration. The aqueous mother liquor was then extracted with methylene chloride (3 x 50.0ml) but gave no material.

Neutralisation of the aqueous mother liquor by addition of 2M aqueous hydrochloric acid then solid sodium acetate followed by rotary evaporation and extraction of the residue with boiling ethyl acetate (100ml) gave only an intractable orange solid (1.1g), m.p. >360° (decomp.), whose i.r. spectrum suggested that it was inorganic material.

Ethyl 4,7-Dihydroisoxazolo[4,3-b]pyridine-3-carboxylate (189)

A stirred solution of ethyl isoxazolo[4,3-b]pyridine-3-carboxylate (103a) (0.38g; 0.002mol) in 1,4-dioxane (5.0ml) was treated dropwise with a solution of

sodium borohydride (0.33g; 0.0088mol) in water (5.0ml) over 15 min then the resulting suspension was diluted with water (5.0ml) and the mixture stirred at room temperature for 3h.

The mixture was rotary evaporated, the residue treated with water (10.0ml) and the insoluble solid was collected to afford ethyl 4,7-dihydroisoxazolo [4,3-b]pyridine-3-carboxylate (189) (0.07g; 18%) which formed tan, irregular crystals, m.p. 116-118° (from hexane-toluene), ν_{max} 3380 (NH) and 1670 (C=O) cm^{-1}, δ_H ($CDCl_3$) 6.61 (1H, dt, J = 10 and 2 Hz, CH), 6.10 (1H, dtd, J = 10, 4 and 2 Hz, CH), 4.67-4.33 (1H, bs, NH) (exch.), 4.37-4.27 (2H, m, CH_2), 4.34 (2H, q, J = 7 Hz, CH_2) and 1.36 (3H, t, J = 7 Hz, CH_3).

Neutralisation of the aqueous mother liquor by addition of concentrated hydrochloric acid then solid sodium acetate followed by rotary evaporation and extraction of the residue with boiling ethyl acetate (2 x 100ml) gave no further material.

Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188)

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-hydroxyethanoate (187) (23.5g; 0.12mol) in anhydrous acetonitrile (600ml) was treated with activated manganese dioxide (Aldrich 21,764-6) (60.0g) and the resulting suspension was stirred at room temperature with exclusion of atmospheric moisture for 6h.

The mixture was filtered through celite and rotary evaporated to afford ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (20.7g; 89%) as a yellow oil, b.p. 80°/ 0.1mmHg, ν_{max} 3462 and 3255 (NH) and 1730 and 1663 (C=O) cm^{-1}, δ_H ($CDCl_3$) 7.92 (1H, dd, J = 4 and 2 Hz, ArH), 7.22-6.92 (2H, m, 2 x ArH), 6.26 (2H, bs, NH_2) (exch.), 4.36 (2H, q, J = 7 Hz, CH_2) and 1.31 (3H, t, J = 7 Hz, CH_3).

Diethyl 2-Oxobutane-1,4-dioate

Diethyl 2-oxobutane-1,4-dioate was prepared by the sodium ethoxide catalysed condensation of ethyl acetate with diethyl oxalate as described by Wislicenus[125] as a colourless oil (yield 15%), b.p. 80-85°/ 0.3mmHg (lit.,[125] 131-132°/ 24mmHg).

Ethyl 3-Acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a)

(a) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and ethyl 3-oxobutanoate (0.26g; 0.002mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 22h.

The mixture was cooled and filtered to give a brown solid (0.17g) which was flash-chromatographed over silica.

Elution with ethyl acetate afforded ethyl 3-acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a) (0.15g; 29%) which formed colourless needles, m.p. 213-214° (from ethanol), ν_{max} 3100-2500 br (NH,OH) and 1735, 1695 and 1655 (C=O) cm^{-1}, δ_H ($CDCl_3$) 12.6-12.2 (1H, bs, NH or OH) (exch.), 8.66 (1H, dd, J = 4 and 2 Hz, ArH), 7.72 (1H, dd, J = 7 and 2 Hz, ArH), 7.52 (1H, dd, J = 7 and 4 Hz, ArH), 4.53 (2H, q, J = 7 Hz, CH_2), 2.75 (3H, s, CH_3) and 1.41 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only an intractable brown tar (0.03g).

Rotary evaporation of the xylene mother liquor gave a brown oil (0.23g) whose t.l.c. in methylene chloride-ethyl acetate (2:1) showed it to be a five component mixture which was therefore not further investigated.

(b) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and ethyl 3-oxobutanoate (0.26g; 0.002mol) in anhydrous diglyme (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 23h.

The mixture was rotary evaporated to give a dark brown solid (0.52g) which was flash-chromatographed over silica.

Elution with methylene chloride gave unreacted ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.05g; 13%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (2:1) over silica] with an authentic sample.

Elution with ethyl acetate gave a crude solid which was crystallised from ethanol to afford ethyl 3-acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a) (0.08g; 15%) as an orange solid, m.p. 210-211°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Final elution with methanol gave only an intractable black gum (0.17g) which was not further investigated.

(c) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and ethyl 3-oxobutanoate (0.52g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 3h.

The mixture was rotary evaporated to give a brown solid (1.1g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (9:1) gave a two component yellow solid (0.08g) which was not further investigated.

Further elution with methylene chloride-ethyl acetate (9:1) afforded ethyl 3-acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a) (0.90g; 87%) as a pale orange solid, m.p. 209-211°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Final elution with methanol gave only an intractable brown tar (0.06g) which was not further investigated.

(d) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and ethyl 3-oxobutanoate (0.52g; 0.004mol) in anhydrous diglyme (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 7h.

The mixture was rotary evaporated to give a gummy, brown solid (1.5g) which was flash-chromatographed over silica.

Elution with methylene chloride gave unreacted ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.12g; 15%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (2:1) over silica] with an authentic sample.

Elution with ethyl acetate gave a gummy, yellow solid which was washed with diethyl ether to afford ethyl 3-acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a) (0.25g; 24%) as a cream solid, m.p. 209-210°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Rotary evaporation of the ethereal mother liquor gave a multicomponent brown oil (0.35g) which was not further investigated.

Further elution with ethyl acetate and then finally with methanol gave only a series of multicomponent brown oils (total 0.61g) from which no identifiable material could be obtained.

Ethyl 3-Benzoyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191b)

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and ethyl benzoylacetate (0.77g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 2h.

The mixture was rotary evaporated to give a brown gum (1.4g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (1:1) afforded ethyl 3-benzoyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191b) (1.1g; 85%) which formed colourless, irregular crystals, m.p. 201-202° (from ethanol), ν_{max} 3000-2500 br (NH,OH) and 1740 and 1700-1600 (C=O) cm^{-1}, δ_H ($CDCl_3$) 12.6 (1H, bs, NH or OH) (exch.), 8.59 (1H, dd, J = 4 and 2 Hz, ArH), 7.98-7.89 (2H, m, 2 x ArH), 7.60-7.30 5H, m, 5 x ArH), 4.23 (2H, q, J = 7 Hz, CH_2) and 1.06 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only an intractable brown tar (0.20g) which was not further investigated.

Ethyl 2-(4-Ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl)-2-oxoethanoate (191c)

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and diethyl 2-oxobutane-1,4-dioate (0.38g; 0.002mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 1h .

The mixture was rotary evaporated to give a gummy solid which was washed with hexane to afford ethyl 2-(4-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl)-2-oxoethanoate (191c) (0.48g; 75%) which formed pale brown, irregular crystals, m.p. 145-147° (from toluene), ν_{max} 3100-2500 br (NH,OH) and 1750, 1730,1700 and 1660 (C=O) cm^{-1}, δ_H ($CDCl_3$) 12.5 (1H, bs, NH or OH) (exch.), 8.70 (1H, dd, J = 4 and 1 Hz, ArH), 7.65-7.56 (2H, m, 2 x ArH), 4.55 (2H, q, J = 7 Hz, CH_2), 4.42 (2H, q, J = 7 Hz, CH_2), 1.41 (3H, t, J = 7 Hz, CH_3) and 1.38 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the hexane mother liquor gave only a negligible amount of material.

Pyridazino[4,5-c]-1,5-napthyridine-2,6-diones (192a-c)

A solution of the corresponding 1,5-napthyridine derivative (0.001mol) in ethanol (10.0ml) was treated with 100% hydrazine monohydrate (0.05g; 0.001mol) and the mixture was stirred and heated under reflux for 1h then worked up as descrided for the individual reactions below.

(i) 3-Methylpyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione (192a)

The mixture from ethyl 3-acetyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191a) was hot-filtered to afford 3-methylpyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione (192a) (0.20g; 88%) which formed green plates, m.p. >350° (from dimethylsulphoxide), ν_{max} 3300 and 3000-2500 br (NH,OH) and 1700-1630 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 13.2-12.7 (1H, bs, NH or OH) (exch.), 12.5-12.0 (1H, s, NH/OH) (broad, exch.), 8.66-8.59 (1H, m, ArH), 7.68-7.59 (2H, m, 2 x ArH) and 2.90 (3H, s, CH_3).

Rotary evaporation of the organic mother liquor gave no further material.

(ii) 3-Phenylpyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione (192b)

The mixture from ethyl 3-phenyl-1,5-napthyridin-2(1H)-one-4-carboxylate (191b) was hot-filtered to afford 3-phenylpyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione (192b) (62%) which formed a yellow microcrystalline solid, m.p. >350° (from dimethylformamide), ν_{max} 3000-2500 br (NH,OH) and 1650 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 14.0-12.0 (2H, bs, 2 x NH or OH) (exch.), 8.65 (1H, dd, J = 4 and 2 Hz, ArH), 7.82-7.51 (2H, m, 2 x ArH) and 7.37 (5H, s, 5 x ArH).

Rotary evaporation of the organic mother liquor gave a six component yellow solid (0.12g) which was not further investigated.

(iii) Ethyl Pyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione-3-carboxylate (192c)

The mixture from ethyl 2-(4-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl)-2-oxoethanoate (191c) was hot-filtered to afford ethyl pyridazino[4,5-c]-1,5-napthyridine-2,6(1H,5H)-dione-3-carboxylate (192c) (0.10g; 35%) which formed a yellow microcrystalline solid, m.p. 309-313° (decomp.) (from glacial acetic acid-dimethylformamide), ν_{max} 3400-3100 and 3100-2500 br (NH,OH) and 1720 and 1670 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 14.0-12.0 (2H, bs, 2 x NH,OH) (exch.), 8.69 (1H, dd, J = 4 and 2 Hz, ArH), 7.76 (1H, dd, J = 8 and 2 Hz, ArH), 7.66 (1H, dd, J = 8 and 4 Hz, ArH), 4.33 (2H, q, J = 7 Hz, CH_2) and 1.30 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the organic mother liquor gave an unidentified orange solid (0.16g), m.p. 321-330° (decomp.), which was not further investigated.

The Attempted Condensation of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with Diethyl 3-Oxopentane-1,5-dioate

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and diethyl 3-oxopentane-1,5-dioate (0.40g; 0.002mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5Å molecular sieves (30g) for 3h.

The mixture was rotary evaporated to give an intractable brown solid (0.57g), m.p. 52-89°, from which no identifiable material could be obtained.

Attempted Condensation Reactions of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with Ethyl 3-Oxobutanoate

(a) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and ethyl 3-oxobutanoate (0.26g; 0.002mol) in glacial acetic acid (10.0ml) was treated with concentrated sulphuric acid (0.037g; 0.00038mol) and the resulting

mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to *ca* 1ml then diluted with water (5.0ml) and the resulting solution was extracted with methylene chloride (4 x 25.0ml) to give only a black intractable solid (0.16g), m.p. 82-105°, which yielded no identifiable material.

Neutralisation of the aqueous mother liquor with solid sodium acetate followed by extraction with methylene chloride (4 x 25.0ml) gave no further material.

(ii) A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) and ethyl 3-oxobutanoate (0.26g; 0.002mol) in glacial acetic acid (2.0ml) was treated with piperidine (0.20ml) and the resulting mixture was stirred and heated at 60° (oil bath) with exclusion of atmospheric moisture for 24h.

The mixture was diluted with water (5.0ml) and the insoluble solid was collected to give only a black intractable solid (0.09g), m.p.114-250° (decomp.), which yielded no identifiable material.

Extraction of the aqueous mother liquor with methylene chloride (3 x 10.0ml) gave a multicomponent black oil (0.34g) which was not further investigated.

<u>The Condensation of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with Diethyl Propanedioate</u>

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and diethyl propanedioate (0.64g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moistureand with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 8h .

The mixture was rotary evaporated to give a brown gum (1.1g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (4:1) afforded 4-ethoxycarbonyl-1,5-napthyridin-2(1H)-one-3-*N*-(2-ethoxalylpyrid-3-yl)carboxamide (193) (0.43g; 49%) which formed colourless, irregular crystals, m.p. 231-232° (from glacial acetic acid), ν_{max} 3100-2500 br (NH,OH) and 1740-1725, 1680 and 1640 (C=O) cm^{-1}, δ_H ($CDCl_3$) 13.3 (1H, bs, NH or OH) (exch.), 13.2 (1H, bs, NH or OH) (exch.), 9.31 (1H, dd, J = 9 and 1 Hz, ArH), 8.73 (1H, dd, J = 4 and 1 Hz, ArH), 8.48 (1H, dd, J = 4 and 1 Hz, ArH), 8.27 (1H, dd, J = 9 and 1 Hz, ArH), 7.59 (1H, dd, J = 9 and 4 Hz, ArH), 7.56 (1H, dd, J = 9 and 4 Hz, ArH), 4.65 (2H, q, J = 7 Hz, CH_2), 4.47 (2H, q, J = 7 Hz, CH_2), 1.46 (3H, t, J = 7 Hz, CH_3) and 1.39 (3H, t, J = 7 Hz, CH_3), δ_C ($CDCl_3$) 190.0 (quat), 165.9 (quat), 165.4 (quat), 162.8 (quat), 161.7 (quat), 151.7 (quat), 147.7 (CH), 144.4 (CH), 138.3 (quat), 136.2 (quat), 136.0 (quat), 134.3 (quat), 130.3 (CH), 129.2 (CH), 127.5 (CH), 125.0 (CH), 120.3 (quat), 62.3 (CH_2), 62.1 (CH_2), 14.02 (CH_3) and 13.99 (CH_3).

Elution with methylene chloride-ethyl acetate (1:1) afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.25g; 22%) which formed yellow prisms, m.p. 185-187° (from ethyl acetate), ν_{max} 3000-2500 br (NH,OH) and 1740-1720 and 1660-1640 (C=O) cm^{-1}, δ_H ($CDCl_3$) 12.6 (1H, bs, NH or OH) (exch.), 8.63 (1H, dd, J = 4 and 2 Hz, ArH), 7.78 (1H, dd, J = 9 and 2 Hz, ArH), 7.48 (1H, dd, J = 9 and 4 Hz, ArH), 4.65-4.30 (4H, m, 2 x CH_2), 1.41 (3H, t, J = 7 Hz, CH_3) and 1.40 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only an intractable brown gum (0.09g) which was not further investigated.

<u>The Attempted Hydrolysis of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate (195)</u>

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in 2M aqueous sodium hydroxide (5.0ml) was stirred and heated under reflux for 1h.

Neutralisation of the mixture by the addition of 2M aqueous hydrochloric acid then solid sodium acetate followed by extraction with methylene chloride (3 x 10.0ml) gave no material.

Rotary evaporation of the aqueous mother liquor and extraction of the residue with boiling ethyl acetate (2 x 25.0ml) again gave no material.

The Attempted Reaction of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate (195) with Hydrazine in Ethanol

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in ethanol (10.0ml) was treated with 100% hydrazine monohydrate (0.05g; 0.001mol) and the mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 5h.

Rotary evaporation of the mixture gave only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 100%) as a cream solid, m.p. 171-175°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Pyridazino[4,5-c]-1,5-napthyridine-2,3,6(1H,4H,5H)-trione (196)

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in 100% hydrazine monohydrate (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave a red solid (0.23g) which was treated with 2M aqueous hydrochloric acid (4.0ml) and the insoluble solid collected to afford pyridazino[4,5-c]-1,5-napthyridine-2,3,6(1H,4H,5H)-trione (196) (0.096g; 42%) which formed a brown microcrystalline solid, m.p. >350° (from dimethylsulphoxide), ν_{max} 3100-2500 br (NH,OH) and 1710-1680 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 12.8 (1H, bs, NH or OH) (exch.), 8.91-8.08 (1H, m, ArH), 8.12-7.76 (2H, m, 2 x ArH).

Neutralisation of the aqueous mother liquor by the addition of 2M aqueous hydrochloric acid then solid sodium acetate followed by extraction with methylene chloride (3 x 10.0ml) gave no further material.

Ethyl 2-[3-(2-Ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194)

A stirred solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) in anhydrous benzene (5.0ml) was treated dropwise with a solution of ethyl malonyl chloride (0.30g; 0.002mol) in anhydrous benzene (5.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to afford ethyl 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194) (0.61g; 99%) as a brown oil, ν_{max} 3300 (NH) and 1740 and 1685 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.5-11.0 (1H, bs, NH) (exch.), 9.05 (1H, dd, J = 9 and 2 Hz, ArH), 8.39 (1H, dd, J = 4 and 2 Hz, ArH), 7.48 (1H, ddd, J = 9, 4 and 0.4 Hz, ArH), 4.56-4.12 (4H, m, 2 x CH_2) 1.36 (3H, t, J = 7 Hz, CH_3) and 1.28 (3H, t, J = 7 Hz, CH_3), which could not be further purified by high vacuum distillation due to its thermal instability.

Attempted purification of ethyl 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194) (0.25g) by dry flash-chromatography in hexane-ethyl acetate (1:1) over silica afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.20g; 85%) as a colourless solid, m.p. 175-178°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

The Attempted Cyclisation of Ethyl 2-[3-(2-Ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194) Using Ethanolic Sodium Ethoxide

A solution of ethyl 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194) (0.62g; 0.002mol) in anhydrous ethanol (5.0ml) was treated with a solution of sodium (0.18g; 0.008g.atom) in anhydrous ethanol (5.0ml) and the

resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue was treated with water (5.0ml) and the resulting solution was acidified with 2M aqueous hydrochloric acid. The insoluble solid was collected to give an intractable brown solid (0.10g), m.p. 250° (decomp.), from which no identifiable material could be obtained.

The aqueous mother liquor was extracted with methylene chloride (4 x 10.0ml) but gave only a multicomponent, brown gum (0.27g) which was not further investigated.

Neutralisation of the aqueous mother liquor by addition of solid sodium acetate followed by rotary evaporation and extraction of the residue with boiling ethyl acetate (2 x 50.0ml) gave no further material.

Diethyl 1,5-Napthyrid-2(1H)-one-3,4-dicarboxylate (195)

A solution of ethyl 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanoate (194) (45.6g; 0.15mol) in anhydrous ethanol (750ml) was treated with anhydrous triethylamine (60.0g; 0.60mol) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

Rotary evaporation of the mixture gave a gummy, brown solid which was washed with ethanol (150ml) to afford diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (29.3g; 67%) as an orange solid, m.p. 185-187°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethanolic mother liquor gave a viscous, black gum (14.5g) from which no identifiable material was obtained.

The Attempted Condensation of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with Ethyl 2-Cyanoethanoate

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and ethyl 2-cyanoethanoate (0.45g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 27h.

The mixture was rotary evaporated to give a brown oil (1.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave unreacted ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.40g; 51%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Further elution with hexane-ethyl acetate (1:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and tars (total 0.63g) which were not further investigated.

2-Cyanoethanoyl Chloride

2-Cyanoethanoyl chloride was prepared by the reaction of 2-cyanoethanoic acid with phosphorous pentachloride as described by Weaver[58] as a yellow oil (yield 100%), ν_{max} 2267 (CN) and 1794 (C=O) cm^{-1}.

Attempted Reactions of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with 2-Cyanoethanoyl Chloride

(a) A stirred solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.39g; 0.002mol) in anhydrous benzene (5.0ml) was treated dropwise with a solution of 2-cyanoethanoyl chloride (0.20g; 0.002mol) in anhydrous benzene (5.0ml) and the

resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave only a black intractable solid (0.48g), m.p. >360°, from which no identifiable material was obtained.

(b) A stirred solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.77g; 0.004mol) and triethylamine (0.40g; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was cooled to 15° (ice-water bath) then treated dropwise with a solution of 2-cyanoethanoyl chloride (0.41g; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml). The resulting solution was then stirred at room temperature with exclusion of atmospheric moisture for 22h.

The mixture was filtered to remove triethylamine hydrochloride and the mother liquor was rotary evaporated and the residue treated with water (5.0ml). The resulting solution was extracted with methylene chloride (3 x 10.0ml) to give a dark brown gum (0.90g) whose t.l.c. in hexane-ethyl acetate (3:7) over silica showed it to be a six component mixture which was therefore not further investigated.

Ethyl 2-[3-(2-Phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199)

A stirred solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.97g; 0.005mol) in anhydrous benzene (12.5ml) was treated dropwise with a solution of 2-phenylethanoyl chloride (0.77g; 0.005mol) in anhydrous benzene (12.5ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave a brown gum (1.7g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded ethyl 2-[3-(2-phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199) (1.2g; 72%) which formed colourless plates, m.p. 80-81° (from ethanol), ν_{max} 3305 (NH) and 1732, 1712 and

1668 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.0-10.3 (1H, bs, NH) (exch.), 9.10 (1H, dd, J = 9 and 1 Hz, ArH), 8.36 (1H, dd, J = 4 and 1 Hz, ArH), 7.46 (1H, dd, J = 9 and 4 Hz, ArH), 7.37 (5H, m, 5 x ArH), 4.42 (2H, q, J = 7 Hz, CH_2), 3.79 (2H, s, CH_2) and 1.37 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (3:2) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and gums (total 0.37g) which were not further investigated.

Attempted Cyclisation Reactions of Ethyl 2-[3-(2-Phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199)

(a) A solution of ethyl 2-[3-(2-phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199) (0.62g; 0.002mol) in anhydrous ethanol (10.0ml) was treated with a solution of sodium (0.18g; 0.008g.atom) in anhydrous ethanol (5.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue was treated with water (10.0ml) and the resulting solution was neutralised by addition of 2M aqueous hydrochloric acid followed by solid sodium acetate and extracted with methylene chloride (3 x 10.0ml) to give a multicomponent brown oil (0.20g) from which no identifiable material could be obtained.

Rotary evaporation of the aqueous phase followed by extraction of the residue with boiling ethyl acetate (2 x 50.0ml) gave only a complex brown oil (0.12g) which was not further investigated.

(b) A solution of ethyl 2-[3-(2-phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199) (0.62g; 0.002mol) in anhydrous ethanol (10.0ml) was treated with triethylamine (0.81g; 0.008mol) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

Rotary evaporation of the mixture gave a brown gum (0.65g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave only unreacted ethyl 2-[3-(2-phenylethanoylamino)pyrid-2-yl]-2-oxoethanoate (199) (0.21g; 34%) as a tan solid, m.p. 80-82°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Further elution with hexane-ethyl acetate (7:3) and then finally with methanol gave only a series of multicomponent oils and gums (total 0.39g) which were not further investigated.

Ethyl 2-[3-(2-Chloroethanoylamino)pyrid-2-yl]-2-oxoethanoate (202)

A stirred solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (7.8g; 0.04mol) in anhydrous toluene (100ml) was treated dropwise with a solution of 2-chloroethanoyl chloride (4.5g; 0.04mol) in anhydrous toluene (100ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave a black gum (10.5g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanoate (202) (9.3g; 86%) which formed colourless needles, m.p. 62-63° (from hexane-ethyl acetate), ν_{max} 3260 (NH) and 1740, 1700 and 1670 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.6 (1H, bs, NH or OH) (exch.), 9.10 (1H, dd, J = 9 and 1 Hz, ArH), 8.47 (1H, dd, J = 5 and 1 Hz, ArH), 7.55 (1H, dd, J = 9 and 5 Hz, ArH), 4.47 (2H, q, J = 7 Hz, CH_2), 4.22 (2H, s, CH_2) and 1.36 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (7:3) and then finally with methanol gave only a series of multicomponent oils and gums (total 0.67g) which were not further investigated.

Ethyl 3-Benzenesulphonyl-1,5-napthyridin-2(1H)-one-4-carboxylate (205)

A solution of ethyl 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanoate (202) (1.1g; 0.004mol) and sodium benzenesulphinate (0.72g; 0.0044mol) in ethanol (40.0ml) was stirred and heated under reflux for 4h.

The mixture was rotary evaporated, the residue treated with water (20.0ml) and the resulting solution was extracted with methylene chloride (3 x 20.0ml) to give a yellow gum (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave unreacted ethyl 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanoate (202) (0.69g; 63%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Elution with hexane-ethyl acetate (1:4) afforded ethyl 3-benzenesulphonyl-1,5-napthyridin-2(1H)-one-4-carboxylate (205) (0.63g; 44%) which formed colourless prisms, m.p. 222-224° (from glacial acetic acid), ν_{max} 3100-2500 br (NH,OH) and 1754, 1724 and 1671 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 13.5-11.5 (1H, bs, NH or OH) (exch.), 8.63 (1H, dd, J = 4 and 2 Hz, ArH), 8.03-7.99 (2H, m, 2 x ArH), 7.78-7.61 (5H, m, 5 x ArH), 4.51 (2H, q, J = 7 Hz, CH_2), and 1.40 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

N-[3-Ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl]pyridinium Chloride (206)

A solution of ethyl 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanoate (202) (10.3g; 0.038mol) in anhydrous pyridine (95.0ml) was stirred and heated at 100° (oil bath) with exclusion of atmospheric moisture for 0.5h.

The mixture was rotary evaporated to give a waxy solid which was washed with anhydrous diethyl ether (100ml) to afford *N*-[3-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl]pyridinium chloride (206) (12.2g; 97%) which formed cream, irregular crystals, m.p. 230-232° (decomp.) (from ethanol), ν_{max} 2900-2500 br (NH,OH) and 1735 and 1677 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 13.7-13.1 (1H, bs, NH or OH) (exch.),

9.30 (2H, dd, J = 7 and 1 Hz, 2 x ArH), 9.06-8.87 (1H, m, ArH), 8.68 (1H, dd, J = 4 and 2 Hz, ArH), 8.57-8.38 (2H, m, 2 x ArH), 8.09 (1H, dd, J = 9 and 2 Hz, ArH), 7.80 (1H, dd, J = 9 and 4 Hz, ArH), 4.22 (2H, q, J = 7 Hz, CH_2), and 1.01 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the ethereal mother liquor gave no further material.

Ethyl 3-Amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207)

A solution of *N*-[3-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl]pyridinium chloride (206) (8.6g; 0.026mol) in anhydrous methanol (65.0ml) was treated with piperidine (65.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated to give a brown gum (17.0g) which was dry flash-chromatographed over silica.

Elution with ethyl acetate afforded ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (6.0g; 99%) which formed brown needles, m.p. 192-194° (from methanol), ν_{max} 3475 and 3345 (NH), 3100-2500 br (NH,OH) and 1670 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 12.5-11.7 (1H, bs, NH or OH) (exch.), 8.31 (1H, dd, J = 5 and 2 Hz, ArH), 7.54 (1H, dd, J = 8 and 2 Hz, ArH), 7.17 (1H, dd, J = 8 and 5 Hz, ArH), 6.40 (2H, bs, NH) (exch.), 4.34 (2H, q, J = 7 Hz, CH_2), and 1.30 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave an intractable brown gum (3.0g) which was not further investigated.

The Attempted Reaction of Ethyl 2-(3-Aminopyrid-2-yl)-2-oxoethanoate (188) with Dimethyl But-2-ynedioate

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.78g; 0.004mol) and dimethyl but-2-ynedioate (0.59g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture

and with cycling of the solvent through a soxhlet extractor containing anhydrous 5Å molecular sieves (30g) for 23h.

The mixture was rotary evaporated to give a brown gum (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (0.68g; 87%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Final elution methanol gave only an intractable brown tar (0.43g) which was not further investigated.

2-(3-Aminopyrid-2-yl)-2-oxoethanenitrile (208)

A solution of 3-cyanoisoxazolo[4,3-b]pyridine (106d) (7.3g; 0.05mol) in ethyl acetate (200ml) was hydrogenated over 10% palladium-on-charcoal (0.73g) at room temperature and atmospheric pressure for 4.5h. Further 10% palladium-on-charcoal (0.73g) was added and the mixture was hydrogenated for a further 9.5h.

The mixture was filtered through celite and was rotary evaporated to give a gummy solid. This was washed with hexane to afford 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (6.7g; 92%) which formed brown, irregular crystals, m.p. 143-146° (from hexane-toluene), ν_{max} 3428, 3318 and 3189 (NH), 2221 (CN) and 1648 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.20 (1H, dd, J = 4 and 1 Hz, ArH), 7.33 (1H, dd, J = 9 and 4 Hz, ArH), 7.08 (1H, dd, J = 9 and 4 Hz, ArH) and 6.35-6.11 (2H, bs, NH_2) (exch.), δ_C [$(CD_3)_2S$=O] 168.3 (quat), 150.3 (quat), 139.6 (CH), 130.9 (CH), 130.2 (quat), 125.7 (CH) and 115.1 (quat).

Rotary evaporation of the organic mother liquor gave a three component brown oil (0.39g) which was not further investigated.

3-Aminopyridine-2-carboxylic Acid (93)

A solution of 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (0.29g; 0.002mol) in glacial acetic acid (7.0ml) and water (3.0ml) was stirred and heated at the corresponding temperature for the corresponding time then worked up as described for the individual reactions below.

(i) The mixture from the reaction at room temperature for 4h was rotary evaporated to give a brown gum (0.38g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave unreacted 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (0.099g; 34%) as a yellow gum identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Further elution with ethyl acetate afforded 3-aminopyridine-2-carboxylic acid (93) (0.13g; 46%) as a yellow solid, m.p. 205° (decomp.) [lit.,[126] 211-212° (decomp.)], ν_{max} 3500-2000 br (NH and OH), 1667 (C=O) and 1647 cm^{-1}, δ_H [$(CD_3)_2S$=O] 8.5-6.7 (3H, bs, NH_2 and OH) (exch.), 7.83 (1H, dd, J = 4 and 2 Hz, ArH) and 7.33-7.29 (2H, m, 2 x ArH).

Final elution with methanol gave a negligible amount of material.

(ii) The mixture from the reaction at reflux for 1h was rotary evaporated to give a brown gum (0.38g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave an intractable, multicomponent brown gum (0.10g) which was not further investigated.

Further elution with ethyl acetate afforded 3-aminopyridine-2-carboxylic acid (93) (0.19g; 69%) as a yellow solid, m.p. 205° (decomp.) [lit.,[126] 211-212° (decomp.)], identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a negligible amount of material.

Ethyl 3-Aminopyridine-2-carboxylate (209)

A solution of 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (0.29g; 0.002mol) in anhydrous ethanol (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 4h.

The mixture was rotary evaporated to give a brown gum (0.25g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) afforded ethyl 3-aminopyridine-2-carboxylate (209) (0.25g; 75%) which formed pale orange needles, m.p. 127-129° (from toluene), ν_{max} 3418, 3275 and 3160 (NH) and 1697 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.06 (1H, dd, J = 4 and 2 Hz, ArH), 7.19 (1H, dd, J = 8 and 4 Hz, ArH), 6.99 (1H, dd, J = 8 and 2 Hz, ArH), 5.87-5.55 (2H, bs, NH_2) (exch.), 4.43 (2H, q, J = 7 Hz, CH_2) and 1.42 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a negligible amount of material.

The Reaction of 2-(3-Aminopyrid-2-yl)-2-oxoethanenitrile (208) with Ethyl Malonyl Chloride

A stirred solution of 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (0.74g; 0.005mol) in anhydrous benzene (12.5ml) was treated dropwise with a solution of ethyl malonyl chloride (0.74g; 0.002mol) in anhydrous benzene (12.5ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to afford 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (210a) (1.2g; 92%) as a brown gum, ν_{max} 3186 (NH), 2220 (CN) and 1720 and 1674 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.2 (1H, bs, NH) (exch.), 9.09 (1H, dd, J = 9 and 1 Hz, ArH), 8.55 (1H, dd, J = 4 and 1 Hz, ArH), 7.60 (1H, dd, J = 9 and 4 Hz, ArH), 4.26 (2H, q, J = 7 Hz, CH_2), 3.54 (2H, s, CH_2) and 1.29 (3H, t, J = 7 Hz, CH_3), which could not be further purified by high vacuum distillation or by flash-chromatography.

Attempted trituration of crude 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (210a) (0.52g) with ethyl acetate gave 3-(2-ethoxycarbonylethanoylamino)pyridine-2-carboxylic acid (210b) (0.14g; 28%) which formed brown plates, m.p. 172-173° (decomp.) (from ethanol-glacial acetic acid), ν_{max} 3100-2500 br (NH and OH) and 1736, 1694 and 1670 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 11.4 (1H, bs, NH) (exch.), 8.79 (1H, dd, J = 9 and 1 Hz, ArH), 8.40 (1H, dd, J = 5 and 1 Hz, ArH), 7.67 (1H, dd, J = 9 and 5 Hz, ArH), 4.15 (2H, q, J = 7 Hz, CH_2), 3.62 (2H, s, CH_2) and 1.22 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the organic mother liquor gave an intractable, multicomponent brown oil (0.15g) which was not further investigated.

Ethyl 4-Cyano-1,5-napthyridin-2(1H)-one-3-carboxylate (211)

(a) A solution of 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (210a) (1.0g; 0.004mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was treated with anhydrous triethylamine (2.0g; 0.02mol) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated to give a black oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) afforded ethyl 4-cyano-1,5-napthyridin-2(1H)-one-3-carboxylate (211) (0.19g; 20%) which formed yellow plates, m.p. 240-242° (from ethanol-glacial acetic acid), ν_{max} 3100-2500 br (NH,OH) and 1747 and 1652 (C=O) cm^{-1}, δ_H ($CDCl_3$) 13.0-11.5 (1H, bs, NH or OH) (exch.), 8.77 (1H, dd, J = 4 and 2 Hz, ArH), 7.81 (1H, dd, J = 9 and 2 Hz, ArH), 7.59 (1H, dd, J = 9 and 4 Hz, ArH), 4.56 (2H, q, J = 7 Hz, CH_2) and 1.48 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave a complex brown gum (0.50g) from which no identifiable material could be obtained.

(b) A solution of 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (210a) (1.1g; 0.0042mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was treated with anhydrous triethylamine (2.1g; 0.021mol) and the resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated to give a dark brown gum (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) afforded ethyl 4-cyano-1,5-napthyridin-2(1H)-one-3-carboxylate (211) (0.27g; 27%) as an orange solid, m.p. 230-236°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a brown gum (0.82g) which was treated with 2M aqueous hydrochloric acid (2.0ml) then with methylene chloride (10.0ml) and the insoluble solid collected to afford 3-(2-ethoxycarbonylethanoylamino)pyridine-2-carboxylic acid (210b) (0.079g; 7%) as a brown solid, m.p. 164-167° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

The two phase mother liquor was separated and the aqueous phase further extracted with methylene chloride (2 x 10.0ml) then the combined extracts were rotary evaporated to give only a small amount of an intractable brown gum from which no identifiable material could be obtained.

(c) A solution of 2-[3-(2-ethoxycarbonylethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (210a) (1.2g; 0.0046mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was treated with anhydrous *N,N*-diisopropylethylamine (3.0g; 0.023mol) and the resulting mixture was stirred at room temperature with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated to give a brown gum (1.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:7) afforded ethyl 4-cyano-1,5-napthyridin-2(1H)-one-3-carboxylate (211) (0.18g; 16%) as an orange solid, m.p. 234-238°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a intractable dark brown gum (1.0g) from which no identifiable material could be obtained.

6-Aminopyridazino[4,5-c]-1,5-napthyridine-2,3(1H,4H)-dione (212)

A solution of 4-cyano-1,5-napthyridin-2(1H)-one-3-carboxylate (211) (0.24g; 0.001mol) in ethanol (10.0ml) was treated with 100% hydrazine monohydrate (0.05g; 0.001mol) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The resulting suspension was hot-filtered to afford 6-aminopyridazino[4,5-c]-1,5-napthyridine-2,3(1H,4H)-dione (212) as a pale orange powder, m.p. >360°, ν_{max} 3328, 3229 and 3172 (NH), 3100-2500 br (NH,OH) and 1705 (C=O) cm^{-1}, which could not be further purified by crystallisation or precipitation and whose ^1H n.m.r. spectrum could not be recorded due to its low solubility in both organic and aqueous solvents, .

Rotary evaporation of the ethanolic mother liquor gave a complex orange gum (0.09g) which was not further investigated.

Reactions of 2-(3-Aminopyrid-2-yl)-2-oxoethanenitrile (208) with 2-Chloroethanoyl Chloride

A stirred solution of 2-(3-aminopyrid-2-yl)-2-oxoethanenitrile (208) (0.88g; 0.006mol) in either toluene or benzene (15.0ml) was treated dropwise with a solution of 2-chloroethanoyl chloride (0.68g; 0.006mol) in either toluene or benzene (15.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h then worked up as described for the individual reactions below.

(i) The mixture from the reaction in toluene was rotary evaporated to give a complex, dark brown solid (1.1g) from which no identifiable material could be obtained.

(ii) The mixture from the reaction in benzene was cooled and filtered to give a brown solid (0.38g), m.p. >360°, from which no identifiable material could be obtained.

Rotary evaporation of the organic mother liquor afforded 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (213) (0.63g; 47%) which formed tan needles, m.p. 123-124° (from cyclohexane-toluene), ν_{max} 3288 (NH), 2219 (CN) and 1691 and 1665 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.3 (1H, bs, NH) (exch.), 9.15 (1H, dd, J = 9 and 1 Hz, ArH), 8.63 (1H, dd, J = 4 and 1 Hz, ArH), 7.66 (1H, ddd, J = 9, 4 and 1 Hz, ArH) and 4.22 (2H, s, CH_2).

The Attempted Reaction of 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (213) with Pyridine

A solution of 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanenitrile (213) (0.22g; 0.001mol) in anhydrous pyridine (2.5ml) was stirred and heated at 100° (oil bath) with exclusion of atmospheric moisture for 0.5h.

Rotary evaporation of the mixture gave only an intractable, multicomponent brown gum (0.18g) from which no identifiable material could be obtained.

Isoxazolo[4,3-b]pyridine-3-carboxamide (215)

3-Cyanoisoxazolo[4,3-b]pyridine (106d) (5.8g; 0.04mol) was added portionwise over 15 min to stirred concentrated sulphuric acid (24.0ml) at 0° (ice-salt bath) and the resulting dark solution was stirred at room temperature for 19h.

The mixture was treated with ice (200g) and the resulting solution was neutralised by the addition of 6M aqueous sodium hydroxide followed by glacial acetic acid. The precipitated solid was collected to afford isoxazolo[4,3-b]pyridine-3-carboxamide (215) (5.6g; 86%) which formed tan needles, m.p. 220-222° (from water), ν_{max} 3415 and 3320-3100 br (NH), 1710 (C=O) and 1675 cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.81 (1H, dd, J = 4 and 1 Hz, ArH), 8.44 (1H, bs, NH) (exch.), 8.33 (1H, dd, J = 9 and 1 Hz, ArH), 8.05 (1H, bs, NH) (exch.) and 7.53 (1H, dd, J = 9 and 4 Hz, ArH).

2-(3-Aminopyrid-2-yl)-2-hydroxyethanamide (216)

A solution of isoxazolo[4,3-b]pyridine-3-carboxamide (215) (5.7g; 0.035mol) in dimethylformamide (250ml) was hydrogenated over 10% palladium-on-charcoal (0.57g) at room temperature and atmospheric pressure for 3h.

The mixture was filtered through celite and rotary evaporated to afford 2-(3-aminopyrid-2-yl)-2-hydroxyethanamide (216) (5.6g; 96%) which formed tan plates, m.p. 132-133° (from ethanol), ν_{max} 3445 and 3300 (NH) and 3300-3100 and 3100-2500 br (NH and OH) cm^{-1}, δ_H [$(CD_3)_2S$=O] 7.80 (1H, t, J = 3 Hz, ArH), 7.55 (1H, bs, NH) (exch.), 7.44 (1H, bs, NH) (exch.), 7.07 (2H, d, J = 3 Hz, 2 x ArH), 6.02 (1H, bs, OH) (exch.), 5.47 (2H, bs, NH_2) (exch.) and 5.00 (1H, S, CH).

2-(3-Aminopyrid-2-yl)-2-oxoethanamide (217)

A solution of 2-(3-aminopyrid-2-yl)-2-hydroxyethanamide (216) (0.67g; 0.004mol) in dimethylformamide (20.0ml) was treated with activated manganese dioxide (Aldrich 21,764-6) (2.0g) and the resulting suspension was stirred at room temperature with exclusion of atmospheric moisture for 4h. Further activated manganese dioxide (2.0g) was added and the resulting suspension was stirred at room temperature with exclusion of atmospheric moisture for a further 5h.

The mixture was filtered through celite and the filtrate was rotary evaporated to give a brown oil which was triturated with ethyl acetate to afford 2-(3-aminopyrid-2-yl)-2-oxoethanamide (217) (0.36g; 55%) which formed pale yellow needles, m.p. 166-167° (from ethanol-water), ν_{max} 3495, 3375 and 3180 (NH) and 1665 and 1630 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 7.93-7.87 (2H, m, 2 x ArH), 7.50 (1H, bs, NH) (exch.), 7.30-7-18 (2H, m, ArH and NH) (1 x exch.) and 7.17 (2H, bs, NH_2) (exch.).

Rotary evaporation of the organic mother liquor gave a brown oil (0.20g) which could not be further triturated to obtain solid material but whose t.l.c. in ethyl acetate over silica and i.r. spectrum showed it to be further 2-(3-aminopyrid-2-yl)-2-oxoethanamide (217) (30%) by comparison with a sample prepared before.

The Attempted Reaction of 2-(3-Aminopyrid-2-yl)-2-oxoethanamide (217) with Ethyl Malonyl Chloride

A stirred solution of 2-(3-aminopyrid-2-yl)-2-oxoethanamide (217) (0.33g; 0.002mol) in anhydrous benzene (5.0ml) was treated dropwise with a solution of ethyl malonyl chloride (0.30g; 0.002mol) in anhydrous benzene (5.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to give a multicomponent brown gum (0.59g) from which no identifiable material could be obtained.

Ethyl 2-[3-(2-Chloroethanoylamino)pyrid-2-yl]-2-oxoethanamide (219)

A stirred solution of 2-(3-aminopyrid-2-yl)-2-oxoethanamide (217) (0.33g; 0.002mol) in anhydrous toluene (5.0ml) was treated dropwise with a solution of 2-chloroethanoyl chloride (0.23g; 0.002mol) in anhydrous toluene (5.0ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave a yellow solid (0.33g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:4) afforded ethyl 2-[3-(2-chloroethanoylamino)pyrid-2-yl]-2-oxoethanamide (219) (0.15g; 31%) which formed colourless needles, m.p. 199-201° (decomp.) (glacial acetic acid), ν_{max} 3370 and 3170 (NH) and 1710, 1680 and 1660 (C=O) cm^{-1}, δ_H [$(CD_3)_2S$=O] 11.3 (1H, bs, NH) (exch.), 8.78 (1H, dd, J = 9 and 1 Hz, ArH), 8.51 (1H, dd, J = 5 and 1 Hz, ArH), 8.09 (1H, bs, NH) (exch.), 7.81 (1H, bs, NH) (exch.), 7.73 (1H, dd, J = 9 and 5 Hz, ArH) and 4.51 (2H, s, CH_2).

Final elution with methanol gave a multicomponent, gummy yellow solid (0.27g) which was not further investigated.

Ethyl 2-(3-Aminopyrid-4-yl)-2-oxoethanoate (220)

A solution of ethyl isoxazolo[3,4-c]pyridine-3-carboxylate (112) (9.0g; 0.05mol) in ethyl acetate (100ml) was hydrogenated over 10% palladium-on-charcoal (0.90g) at room temperature and atmospheric pressure for 3h.

The mixture was filtered through celite and rotary evaporated to give a brown oil (9.2g) which was flash-chromatographed over silica.

Elution with methylene chloride and then with methylene chloride-ethyl acetate (9:1) afforded ethyl 2-(3-aminopyrid-4-yl)-2-oxoethanoate (220) which formed a yellow microcrystalline solid, m.p. 70-72° (from hexane-toluene), ν_{max} 3426, 3269 and 3111 (NH) and 1727 and 1658 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.22 (1H, s, ArH), 7.82 (1H, d, J = 5 Hz, ArH), 7.28 (1H, d, J = 5 Hz, ArH), 7.9-6.9 (2H, bs, NH_2) (exch.), 4.37 (2H, q, J = 7 Hz, CH_2) and 1.33 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only an intractable brown gum (2.0g) from which no identifiable material could be obtained.

Ethyl 3-Acetyl-1,7-napthyridin-2(1H)-one-4-carboxylate (221)

A solution of ethyl 2-(3-aminopyrid-4-yl)-2-oxoethanoate (220) (0.78g; 0.004mol) and ethyl 3-oxobutanoate (0.52g; 0.004mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 2h.

The mixture was cooled to 5° (ice bath) and the insoluble solid was collected to afford ethyl 3-acetyl-1,7-napthyridin-2(1H)-one-4-carboxylate (221) (0.63g; 63%) which formed purple, irregular crystals, m.p. 221-222° (decomp.) (from methanol-dimethylformamide), ν_{max} 3100-2500 br (NH) and 1733, 1691 and 1669 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 8.75 (1H, s, ArH), 8.40 (1H, d, J = 6 Hz, ArH), 7.64 (1H, d, J = 6 Hz, ArH), 4.37 (2H, q, J = 7 Hz, CH_2), 2.54 (3H, s, CH_3) and 1.29 (3H, t, J = 7 Hz, CH_3).

Diethyl 1,7-Napthyridin-2(1H)-one-3,4-dicarboxylate (222)

A stirred solution of ethyl 2-(3-aminopyrid-4-yl)-2-oxoethanoate (220) (0.78g; 0.004mol) in anhydrous benzene (10.0ml) was treated dropwise with a solution of ethyl malonyl chloride (0.60g; 0.004mol) in anhydrous benzene (10.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was hot-filtered to afford diethyl 1,7-napthyridin-2(1H)-one-3,4-dicarboxylate hydrochloride (0.75g; 58%) which formed colourless, plates, m.p. 177-179°, (from ethanol), ν_{max} 3100-2081 br (NH.OH) and 1744, 1731 and 1674 (C=O) cm^{-1}, δ_H $[(CD_3)_2S=O]$ 13.7-12.2 (1H, bs, NH or OH) (exch.), 8.83 (1H, m, ArH), 8.44 (1H, m, ArH), 7.85 (1H, d, J = 6 Hz, ArH), 4.43 (2H, q, J = 7 Hz, CH_2), 4.31 (2H, q, J = 7 Hz, CH_2), 1.32 (3H, t, J = 7 Hz, CH_3) and 1.28 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the organic mother liquor gave a dark brown multicomponent gum (0.29g) which was not further investigated.

A solution of diethyl 1,7-napthyridin-2(1H)-one-3,4-dicarboxylate hydrochloride (0.37g; 0.0011mol) in water (3.0ml) was neutralised by the addition of solid sodium acetate and the insoluble solid was collected to afford diethyl 1,7-napthyridin-2(1H)-one-3,4-dicarboxylate (222) (0.25g; 78%) which formed tan needles, m.p. 176-177° (from ethyl acetate), ν_{max} 3100-2500 br (NH,OH), and 1742, 1733 and 1671 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 8.74 (1H, s, ArH), 8.39 (1H, d, J = 6 Hz, ArH), 7.70 (1H, d, J = 6 Hz, ArH), 4.41 (2H, q, J = 7 Hz, CH_2), 4.29 (2H, q, J = 7 Hz, CH_2), 1.31 (3H, t, J = 7 Hz, CH_3) and 1.27 (3H, t, J = 7 Hz, CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 10.0ml) gave no further material.

Diethyl 2-Chloro-1,5-napthyridine-3,4-dicarboxylate (223)

A stirred mixture of phosphorus oxychloride (76.8g; 0.5mol) and *N,N*-dimethylaniline (9.7g; 0.08 mol) was treated in one portion with diethyl 1-5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (14.5g; 0.05mol) and the resulting solution was stirred at room temperature for 20 min then stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave a black oil which was treated with methylene chloride (100ml) and ice (100g) then the two phases were separated and the aqueous phase further extracted with methylene chloride (4 x 100ml). The combined organic extracts were washed sequentially with water (2 x 50.0ml), 2M aqueous hydrochloric acid (2 x 50.0ml) and 10% w/v aqueous sodium hydrogen carbonate (2 x 50.0ml) then rotary evaporated to give a brown oil (16.0g) which was flash-chromatorgaphed over silica.

Elution with hexane-ethyl acetate (7:3) afforded diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (13.4g; 87%) which formed yellow prisms, m.p. 185-187° (from ethyl acetate), ν_{max} 1735 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.03 (1H, dd, J = 4 and 2 Hz, ArH), 8.30 (1H, dd, J = 9 and 2 Hz, ArH), 7.70 (1H, dd, J = 9 and 4 Hz,

ArH), 4.52 (2H, q, J = 7 Hz, CH_2), 4.46 (2H, q, J = 7 Hz, CH_2) and 1.40 (6H, t, J = 7 Hz, 2 x CH_3).

Final elution with methanol gave an intractable brown gum (1.3g) which was not further investigated.

The Attempted Reaction of Diethyl 2-Chloro-1,5-napthyridine-3,4-dicarboxylate (223) with Ammonia

A solution of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.31g: 0.001mol) in anhydrous diethyl ether (5.0ml) was added dropwise to liquid ammonia (10.0ml) at -78° (solid CO_2-acetone bath) then the cooling bath was removed and the mixture was stirred at room temperature for 17h allowing the ammonia to evaporate.

The residue was treated with water (10.0ml) and the resulting mixture was extracted with diethyl ether (3 x 10.0ml) to give only unreacted diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.25g; 81%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Diethyl 2-Benzylamino-1,5-napthyridine-3,4-dicarboxylate (224)

A solution of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (4.3g; 0.014mol) in anhydrous ethanol (70.0ml) was treated with a solution of benzylamine (3.0g; 0.028mol) in anhydrous ethanol (70.0ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was cooled to 5° (ice bath) and the insoluble solid collected and combined with a second crop obtained by rotary evaporation of the ethanolic mother liquor, treatment of the residue with 10% w/v aqueous sodium hydrogen carbonate (50.0ml), extraction of the resulting mixture with methylene chloride (3 x 50.0ml) and crystallisation of the resulting waxy solid from ethanol, to afford diethyl 2-benzylamino-1,5-napthyridine-3,4-dicarboxylate (224) (total = 4.9g; 92%) which

formed yellow plates, m.p. 117-118° (from ethanol), ν_{max} 3340 (NH) and 1745 and 1705 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.62 (1H, dd, J = 4 and 2 Hz, ArH), 8.35 (1H, bt, NH) (exch.), 7.91 (1H, dd, J = 9 and 2 Hz, ArH), 7.44 (1H, dd, J = 9 and 4 Hz, ArH), 7.38-7.26 (5H, m, 5 x ArH), 4.84 (2H, q, J = 7 Hz, CH_2), 4.53 (2H, q, J = 7 Hz, CH_2), 1.42 (3H, t, J = 7 Hz, CH_3) and 1.37 (3H, t, J = 7 Hz, CH_3).

The Attempted Debenzylation of Diethyl 2-Benzylamino-1,5-napthyridine-3,4-dicarboxylate (224)

A stirred suspension of diethyl 2-benzylamino-1,5-napthyridine-3,4-dicarboxylate (224) (0.38g; 0.001mol) in liquid ammonia (10.0ml) was cooled to -78° (solid CO_2-acetone bath) then treated portionwise over 0.5h with sodium (0.058g; 0.0025g.atom) and the resulting blue soluton was stirred at -78° (solid CO_2-acetone bath) with exclusion of atmospheric moisture for a further 0.5h. The mixture was then treated with ammonium chloride (0.50g) and stirred at room temperature for 17h allowing the ammonia to evaporate.

The residual gum was treated with water (5.0ml) and the mixture neutralised by the addition of 2M aqueous hydrochloric acid followed by solid sodium acetate then was extracted with methylene chloride (3 x 5.0ml) to give an orange oil (0.32g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture which was therefore not further investigated.

Diethyl 2-Benzenesulphonyl-1,5-napthyridine-3,4-dicarboxylate (225)

A solution of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.31g; 0.001mol) in anhydrous dimethylformamide (2.5ml) was added to a stirred solution of sodium benzenesulphinate (0.16g; 0.001mol) in anhydrous dimethylformamide (2.5ml) and the resulting solution was stirred and heated at 100° (oil bath) with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue treated with water (5.0ml) and the resulting solution was extracted with methylene chloride (3 x 5.0ml) to give a yellow oil (0.46g) which was flash-chromatographed over silica.

Elution with hexane-ethhyl acetate (7:3) gave unreacted diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.11g; 35%) as a yellow solid, m.p. 56-64°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (7:3) afforded diethyl 2-benzenesulphonyl-1,5-napthyridine-3,4-dicarboxylate (225) (0.26g; 63%) which formed yellow needles, m.p. 101-102° (from ethanol), ν_{max} 1730 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.11 (1H, dd, J = 4 and 2 Hz, ArH), 8.36 (1H, dd, J = 9 and 2 Hz, ArH), 8.02-7.51 (6H, m, 6x ArH), 4.54 (4H, q, J = 7 Hz, 2 x CH_2), 1.46 (3H, t, J = 7 Hz, CH_3) and 1.41 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

The Attempted Reaction of Diethyl 2-Benzenesulphonyl-1,5-napthyridine-3,4-dicarboxylate (225) with Ammonia

A solution of diethyl 2-benzenesulphonyl-1,5-napthyridine-3,4-dicarboxylate (225) (0.21; 0.0005 mol) was added portionwise to liquid ammonia (10.0ml) at -78° (solid CO_2-acetone bath) then the cooling bath was removed and the mixture stirred at room temperature for 3h giving only unreacted diethyl 2-benzenesulphonyl-1,5-napthyridine-3,4-dicarboxylate (225) (0.20; 95%), as a colourless solid, m.p. 96-99°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Diethyl Tetrazolo[1,5-a]-1,5-napthyridine-4,5-dicarboxylate (227)

A solution of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (8.9g: 0.029mol) in anhydrous dimethylformamide (75.0ml) was added to a stirred suspension of sodium azide (1.9g; 0.029mol) in anhydrous dimethylformamide

(75.0ml) and the resulting solution was stirred and heated at 100° (oil bath) with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue treated with water (150ml) and the suspended solid collected to afford diethyl tetrazolo[1,5-a]-1,5-napthyridine-4,5-dicarboxylate (227) (8.9g; 97%) which formed cream needles, m.p. 162-165° (from ethanol), ν_{max} 1735 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.10 (1H, dd, J = 9 and 2 Hz, ArH), 9.00 (1H, dd, J = 5 and 2 Hz, ArH), 7.90 (1H, dd, J = 9 and 4 Hz, ArH), 4.59 (2H, q, J = 7 Hz, CH_2), 4.57 (2H, q, J = 7 Hz, CH_2), 1.47 (3H, t, J = 7 Hz, CH_3) and 1.43 (3H, t, J = 7 Hz, CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 100ml) gave no further material.

Diethyl 2-Triphenylphosphinimino-1,5-napthyridine-3,4-dicarboxylate (228)

A solution of diethyl tetrazolo[1,5-a]-1,5-napthyridine-4,5-dicarboxylate (227) (0.32g; 0.001mol) in anhydrous 1,4-dioxane (5.0ml) was treated with a solution of triphenylphosphine (0.26g; 0.001mol) in anhydrous 1,4-dioxane (5.0ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave a gummy solid which was washed with hexane to afford diethyl 2-triphenylphosphinimino-1,5-napthyridine-3,4-dicarboxylate (228) (0.54g; 98%) which formed cream, irregular crystals, m.p. 207-208° (from toluene), ν_{max} 1740 and 1710 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.52 (1H, dd, J = 4 and 2 Hz, ArH), 8.04-7.73 (6H, m, 6 x ArH), 7.61-7.14 (11H, m, 11 x ArH), 4.48 (2H, q, J = 7 Hz, CH_2), 4.46 (2H, q, J = 7 Hz, CH_2), 1.31 (3H, t, J = 7 Hz, CH_3) and 1.29 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the hexane mother liquor gave no further material.

Diethyl 2-Amino-1,5-napthyridine-3,4-dicarboxylate (226)

A solution of diethyl 2-triphenylphosphinimino-1,5-napthyridine-3,4-dicarboxylate (228) (11.0g; 0.02mol) in anhydrous 1,4-dioxane (100ml) was treated with 2M aqueous hydrochloric acid (50.0ml) and the resulting solution was stirred and heated at the appropriate temperature with exclusion of atmospheric moisture for the appropriate time then worked up as described for the individual reactions below.

(i) The mixture from the reaction at 50° for 6h was rotary evaporated, the residue treated with water (50.0ml) and the resulting solution was neutralised by the addition of 10% w/v aqueous sodium hydrogen carbonate solution. The resulting suspension was filtered to give a yellow solid (11.1g) which was treated with ethanol (50.0ml) and the insoluble solid collected to afford diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (5.3g; 92%) which formed yellow needles, m.p. 149-150° (from ethanol), ν_{max} 3450, 3430, 3280 and 3150 (NH) and 1735, 1710 and 1695 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.65 (1H, dd, J = 4 and 2 Hz, ArH), 7.84 (1H, dd, J = 9 and 2 Hz, ArH), 7.45 (1H, dd, J = 9 and 4 Hz, ArH), 6.71 (2H, bs, NH_2) (exch.), 4.52 (2H, q, J = 7 Hz, CH_2), 4.40 (2H, q, J = 7 Hz, CH_2), 1.41 (3H, t, J = 7 Hz, CH_3) and 1.38 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the ethanolic mother liquor gave a gummy yellow solid (5.7g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to contain mainly triphenylphosphine oxide and so this solid was not further investigated.

(ii) The mixture from the reaction at room temperature for 94h was rotary evaporated, the residue treated with water and the resulting solution was neutralised by the addition of 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride to afford diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (70%) as a yellow solid, m.p. 145-147°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Diethyl 3,4-Dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229)

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in glacial acetic acid (5.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (2.5ml) and the resulting solution was stirred and heated at 50° for 20h.

The mixture was concentrated by rotary evaporation to one half of its original volume, diluted with water (2.5ml) and the resulting solution was extracted with methylene chloride (3 x 2.5ml) to afford diethyl 3,4-dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) which formed colourless prisms, m.p. 190-193° (decomp.) (from ethanol), ν_{max} 3100-2500 br (NH) and 1772 and 1714 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S{=}O]$ 12.3-10.9 (1H, bs, NH) (exch.), 8.14 (1H, dd, J = 6 and 1 Hz, ArH), 7.53 (1H, dd, J = 9 and 6 Hz, ArH), 7.07 (1H, dd, J = 9 and 1 Hz, ArH), 4.25 (2H, q, J = 7 Hz, CH_2), 4.19 (2H, q, J = 7 Hz, CH_2), 1.20 (3H, t, J = 7 Hz, CH_3) and 1.16 (3H, t, J = 7 Hz, CH_3), $\delta_H[(CD_3)_2S{=}O]$ 161.6 (quat), 160.6 (quat), 136.7 (quat), 134.1 (CH), 128.3 (CH), 126.7 (quat), 113.5 (CH), 62.7 (CH_2), 62.4 (CH_2), 60.4 (quat), 59.6 (quat) and 13.9 (2 x CH_3).

Attempted Reduction Reactions of Diethyl 3,4-Dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229)

A solution of diethyl 3,4-dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) (0.32g; 0.001mol) in water (3.0ml) and either ethanol or glacial acetic acid (7.0ml) was treated with sodium dithionite (0.32g) and the resulting mixture was stirred and heated under reflux for 1h. A second portion of sodium dithionite (0.32g) was added and the mixture was stirred and heated under reflux for a further 1h then worked up as described for the individual reactions below.

(i) The mixture from ethanol was rotary evaporated, the residue treated was with water (5.0ml) and the resulting solution was extracted with methylene chloride (3 x 10.0ml) to give only a multicomponent yellow gum (0.15g) which was not further investigated.

(ii) The mixture from glacial acetic acid was rotary evaporated, the residue was treated with water (5.0ml) and the resulting solution was extracted with methylene chloride (3 x 10.0ml) to give only a brown oil (0.22g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent gums and solids (total 0.20g) which yielded no identifiable material.

The Attempted Hydrolysis of Diethyl 3,4-Dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229)

A solution of diethyl 3,4-dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) (0.32g; 0.001mol) in ethanol (5.0ml) and 2M aqueous hydrochloric acid (2.5ml) was stirred and heated at 50° for 1h.

The mixture was rotary evaporated, the residue treated was with water (5.0ml) and the suspended solid collected to give only unreacted diethyl 3,4-dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) (0.28g; 88%) as a colourless solid, m.p. 197-199° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Diethyl 3,4-Dihydro-3,4-dihydroxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229)

A solution of diethyl 3,4-dihydro-3,4-epoxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) (0.32g; 0.001mol) in 1M aqueous sodium carbonate solution (5.0ml) was stirred at room temperature for 19h.

The mixture was acidified with glacial acetic acid and then subjected to cation-exchange chromatography over Amberlite IR-120 resin to afford diethyl 3,4-dihydro-3,4-dihydroxy-1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (229) (0.32g; 94%) which formed colourless irregular crystals, m.p. 229-230° (decomp.) (from ethanol), ν_{max} 3265 (OH), 3100-2500 br (NH) and 1747, 1728 and 1713 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 10.6 (1H, bs, NH) (exch.), 8.31-8.22 (1H, m, ArH), 7.50 (1H, s, ArH), 7.45 (1H, d, J = 1 Hz, ArH), 5.40 (1H, bs, OH) (exch.), 4.10 (4H, q, J = 7 Hz, 2 x CH_2) and 1.14 (6H, t, J = 7 Hz, 2 x CH_3).

Attempted Oxidation Reactions of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate (195)

(a) A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in glacial acetic acid (5.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (2.5ml) and the resulting mixture was stirred and heated at 50° for 1h.

The mixture was concentrated by rotary evaporation to one half of its original volume and diluted with water (2.5ml) and the insoluble solid was collected to give only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.25g; 86%) as a yellow solid, m.p. 179-186°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride gave no further material.

(b) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in chloroform (5.0ml) was treated dropwise with a solution of 50-55% w/w 3-chloroperbenzoic acid (0.26g; 0.0015mol) in chloroform (5.0ml) and the resulting mixture was stirred and heated at 50° for 2h.

The mixture was washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 2.5ml) and rotary evaporated to give a gummy solid which was washed with a little diethyl ether to afford unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.21g; 72%) as a yellow solid, m.p. 180-185°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(c) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in methanol (10.0ml) was treated with a solution of potassium peroxymonosulphate (OXONE™) (0.61g; 0.001mol) and sodium hydrogen carbonate (0.18g; 0.0022mol) in water (5.0ml) and the resulting mixture was stirred and heated under reflux under a nitrogen atmosphere for 24h.

The resulting suspension was hot-filtered, the filter-cake washed with methanol (3 x 5.0ml) and the mother liquor was rotary evaporated. The residue was treated with water (10.0ml) and the solution obtained was extracted with methylene chloride (3 x 10.0ml) to give unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.20g; 69%) as a yellow solid, m.p. 178-184°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230)

(a) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in chloroform (5.0ml) was treated dropwise with a solution of

50-55% w/w 3-chloroperbenzoic acid (0.26g; 0.0015mol) in chloroform (5.0ml) and the resulting mixture was stirred and heated at 50° for 17h.

The mixture was washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 2.5ml) and rotary evaporated to give an orange gum (0.46g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.15g; 52%) as a yellow solid, m.p. 150-155°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with ethyl acetate-methanol (9:1) afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.15g; 46%) which formed pale yellow, irregular crystals, m.p. 215-217° (from ethanol), ν_{max} 3100-2500 br (NH) and 1746, 1724 and 1714 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 8.15 (1H, dd, J = 6 and 1 Hz, ArH), 7.59 (1H, dd, J = 9 and 6 Hz, ArH), 7.27 (1H, dd, J = 9 and 1 Hz, ArH), 4.26 (4H, q, J = 7 Hz, 2 x CH_2), 1.26 (3H, t, J = 7 Hz, CH_3) and 1.25 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a negligible amount of material.

(b) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in chloroform (5.0ml) was treated dropwise with a solution of 50-55% w/w 3-chloroperbenzoic acid (0.52g; 0.003mol) in chloroform (5.0ml) and the resulting mixture was stirred and heated at 50° for 17h.

The mixture was washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 2.5ml) and rotary evaporated to give a yellow gum (0.62g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.05g; 17%) as a yellow solid, m.p. 180-184°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with ethyl acetate-methanol (9:1) afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.14g; 46%) as a colourless solid, m.p. 202-208°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable yellow gum (0.09g) which was not further investigated.

(c) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (2.9g; 0.01mol) in chloroform (50.0ml) was treated dropwise with a solution of 50-55% w/w 3-chloroperbenzoic acid (8.6g; 0.05mol) in chloroform (50.0ml) and the resulting mixture was stirred and heated at 50° for 17h.

The mixture was washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 25.0ml) and rotary evaporated to give a gummy, yellow solid (7.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) afforded 3-chlorobenzoic acid (3.0g) as an orange solid, m.p. 130-133° (lit.,[127] 158°), identified by comparison [m.p., i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Elution with ethyl acetate-methanol (19:1) gave only unreacted diethyl 1,5-napthyrid-2-one-3,4-dicarboxylate (195) (0.21g; 7%) as a yellow solid, m.p. 180-185°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-methanol (19:1) gave a multicomponent orange gum (0.50g) which was not further investigated.

Further elution with ethyl acetate-methanol (19:1) afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (1.1g; 36%) as a yellow solid, m.p. 206-209°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.42g) which was not further investigated.

(d) A stirred solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate (195) (0.29g; 0.001mol) in chloroform (5.0ml) was treated dropwise with a solution of 50-55% w/w 3-chloroperbenzoic acid (0.52g; 0.0015mol) in chloroform (5.0ml) and the resulting mixture was stirred and heated at 50° for 7h. A second solution of 50-55% w/w 3-chloroperbenzoic acid (0.52g; 0.0015mol) in chloroform (5.0ml) was added and the resulting mixture was stirred and heated at 50° for a further 16h.

The mixture was washed with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 2.5ml) and rotary evaporated to give an gummy, yellow solid (1.1g) which was flash-chromatographed over silica.

Elution with ethyl acetate afforded 3-chlorobenzoic acid (0.39g) as a tan solid, m.p. 137-144° (lit.,[127] 158°), identified by comparison [m.p., i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Further elution with ethyl acetate gave only unreacted diethyl 1,5-napthyrid-2-one-3,4-dicarboxylate (195) (0.08g; 28%) as a yellow solid, m.p. 170-175°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate afforded diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.18g; 59%) as a colourless solid, m.p. 205-210°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only a small amount of a yellow gum (0.03g) which was not further investigated.

<u>The Attempted Reduction of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230)</u>

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.092g; 0.0003mol) in ethanol (3.5ml) and water (1.5ml) was treated with sodium dithionite (0.10g) and the resulting mixture was stirred and heated under reflux

for 1h. A second portion of sodium dithionite (0.10g) was added and the mixture was stirred and heated under reflux for a further1h.

The mixture was rotary evaporated, the residue was treated with water (2.0ml) and the resulting solution was extracted with methylene chloride (3 x 2.0ml) to give a yellow gum (0.085g) whose t.l.c. in ethyl acetate over silica showed it to be a three component mixture which thererfore was not further investigated.

Attempted Oxidation Reactions of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230)

(a) A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in glacial acetic acid (5.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (2.5ml) and the resulting solution was stirred and heated at 50° for 20h.

The mixture was concentrated by rotary evaporation to one half of its original volume, diluted with water (2.5ml) and the resulting solution was extracted with methylene chloride (3 x 5.0ml) to give a yellow gum which was triturated with diethyl ether to give only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.19g; 62%) as a cream solid, m.p. 195-200°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave a multicomponent yellow oil (0.05g) which thererfore was not further investigated.

(b) A stirred solution of 90% w/v aqueous hydrogen peroxide (0.08ml) in anhydrous methylene chloride (2.0ml) was cooled to 5° (ice bath), treated in two portions with trifluoroethanoic anhydride (0.52ml) and the mixture was stirred and allowed to warm to room temperature then treated dropwise with a solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.62g; 0.002mol) in

anhydrous methylene chloride (2.0ml). The resulting soluton was stirred at room temperature with exclusion of atmospheric moisture for 2h, then heated under reflux for 4h and finally stirred at room temperature for a further 17h.

The mixture was rotary evaporated, the residue treated with ice (1.6g) and the resulting solution basified with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride (3 x 10.0ml) to give only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.34g; 56%) as a yellow solid, m.p. 205-209°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(c) A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in pyridine (2.0ml) was treated with 14% w/v aqueous sodium hypochlorite solution (3.0ml) and the resulting mixture was stirred at room temperature for 10 min.

The mixture was diluted with water (10.0ml) and the resulting solution extracted with methylene chloride (3 x 5.0ml). The extracts were washed with 2M aqueous hydrochloric acid (5 x 5.0ml) then with water (2 x 5.0ml) and rotary evaporated to give an orange oil (0.16g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which thererfore was not further investigated.

3-Aminopyridine-2-carboxylic Acid 1-*N*-Oxide (232)

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in 1M aqueous sodium hydroxide (2.5ml) was treated with 30% w/v aqueous hydrogen peroxide solution (0.50ml) and the resulting mixture was stirred at room temperature for 20h.

The mixture was neutralised by the addition of 2M aqueous hydrochloric acid then solid sodium acetate and the resulting solution was extracted with methylene

chloride (3 x 10.0ml) to give 3-aminopyridine-2-carboxylic acid 1-*N*-oxide (232) (0.08g; 53%) as a grey solid, m.p. 167-170° (decomp.), ν_{max} 3424 and 3322 (NH), 3100-2500 br (OH) and 1663 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 7.93 (1H, dd, J = 6 and 1 Hz, ArH), 7.69 (2H, bs, NH_2) (exch.), 7.43 (1H, dd, J = 9 and 6 Hz, ArH) and 7.23 (1H, dd, J = 9 and 1 Hz, ArH).

The Reaction of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) with Acetic Anhydride

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in acetic anhydride (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

Rotary evaporation of the mixture gave a gummy solid which was washed with ethyl acetate to afford diethyl 2,6-diacetoxy-1,5-napthyridine-3,4-dicarboxylate (233) (0.16g; 42%) which formed colourless hexagons, m.p. 153-155° (from ethyl acetate), ν_{max} 1775, 1750 and 1730 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.34 (1H, d, J = 9 Hz, ArH), 7.50 (1H, d, J = 9 Hz, ArH), 4.52 (2H, q, J = 7 Hz, CH_2), 4.38 (2H, q, J = 7 Hz, CH_2), 2.38 (3H ,s, CH_3), 2.37 (3H ,s, CH_3), 1.40 (3H, t, J = 7 Hz, CH_3) and 1.37 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the organic mother liquor gave a brown gum which on standing crystallised to afford diethyl 1,5-napthyridine-2,6(1H,5H)-dione-3,4-dicarboxylate (235) (0.067g; 22%) which formed yellow, irregular crystals, m.p. 264-265° (from glacial acetic acid), ν_{max} 3100-2500 br (NH,OH) and 1725 and 1630 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 12.5-10.5 (2H, bs, 2 x NH or OH) (exch.), 7.66 (1H, d, J = 9 Hz, ArH), 6.59 (1H, d, J = 9 Hz, ArH), 4.34 (2H, q, J = 7 Hz, CH_2), 4.25 (2H, q, J = 7 Hz, CH_2), 1.29 (3H, t, J = 7 Hz, CH_3) and 1.25 (3H, t, J = 7 Hz, CH_3).

Diethyl 1,5-Napthyridine-2,6(1H,5H)-dione-3,4-dicarboxylate (235)

A solution of diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in acetic anhydride (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

Rotary evaporation of the mixture gave a brown gum which was dissolved in ethanol (7.0ml) and water (3.0ml) and the resulting solution was stirred and heated under reflux for 19h.

The mixture was then cooled to 10° (ice bath) and the precipitated solid was collected and combined with a second crop obtained by rotary evaporation of the organic mother liquor followed by trituration of the residue with ethanol to afford diethyl 1,5-napthyridine-2,6(1H,5H)-dione-3,4-dicarboxylate (235) (total 0.21g; 69%) as a yellow solid, m.p. 263-266°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Attempted Reactions of Diethyl 1,5-Napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) with Benzyl Isocyanate and Phenyl Isocyanate

A solution diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.31g; 0.001mol) in anhydrous 1,4-dioxane (2.5ml) was treated with a solution of the corresponding isocyanate (0.0011mol) in anhydrous 1,4-dioxane (2.5ml) and the resulting solution was stirred and heated under reflux with exclusion of atmospheric moisture for 4h then worked up as described for the individual reactions below..

(i) The mixture from benzyl isocyanate was rotary evaporated, the residue was treated with water (10.0ml) and the resulting mixture was extracted with methylene chloride (3 x 10.0ml) to give a gummy solid which was washed with diethyl ether to give only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.19g; 61%) as a yellow solid, m.p. 201-206°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(ii) The mixture from phenyl isocyanate was rotary evaporated, the residue was treated with water (10.0ml) and the resulting mixture was extracted with methylene chloride (3 x 10.0ml) to give a gummy solid which was washed with diethyl ether to give only unreacted diethyl 1,5-napthyridin-2(1H)-one-3,4-dicarboxylate-5-*N*-oxide (230) (0.20g; 65%) as a yellow solid, m.p. 206-209°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of Ethyl 3-Amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) with Potassium Cyanate

A solution of ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.47g; 0.002mol) in 2M aqueous hydrochloric acid (10.0ml) was rotary evaporated then the residue was dissolved in water (6.0ml) and the resulting solution was treated with a solution of potassium cyanate (0.49g; 0.006mol) in water (4.0ml) and then stirred at room temperature for 24h.

Collection of the insoluble solid gave only unreacted ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.17g; 52%) as a brown solid m.p. 200-203°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of Ethyl 3-Amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) with Ethyl Carbamate

A solution of ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.47g; 0.002mol) and ethyl carbamate (0.18g; 0.002mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

The mixture was allowed to cool to room temperature and the insoluble solid was collected and washed with diethyl ether to give only unreacted ethyl 3-amino-1,5-

napthyridin-2(1H)-one-4-carboxylate (207) (0.40g; 85%) as a colourless solid m.p. 190-199°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave a yellow gum whose t.l.c. in hexane-ethyl acetate (1:1) showed in to contain mainly unreacted ethyl carbamate.

The Attempted Reaction of Ethyl 3-Amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) with Cyanamide

A solution of ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.23g; 0.001mol) and cyanamide (0.042g; 0.001mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave only unreacted ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.20g; 87%) as a brown solid m.p. 189-191°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Ethoxycarbonyl Isocyanate

Ethoxycarbonyl isocyanate was prepared by the reaction of ethyl carbamate with oxalyl chloride as described by Lamon[110] as a colourless oil (yield 38%), b.p. 47-50°/ 55mmHg, (lit.,[110] 54-60°/80mmHg.)

1-Ethoxycarbonyl-3-(4-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl)urea (240)

A solution of ethyl 3-amino-1,5-napthyridin-2(1H)-one-4-carboxylate (207) (0.93g; 0.004mol) in anhydrous dimethylformamide (5.0ml) was treated with a solution of ethoxycarbonyl isocyanate (0.46g; 0.004mol) in anhydrous dimethylformamide (5.0ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 18h.

The mixture was rotary evaporated to give a waxy brown solid. This was washed with diethyl ether to afford 1-ethoxycarbonyl-3-(4-ethoxycarbonyl-1,5-

napthyridin-2(1H)-on-3-yl)urea (240) (1.3g; 93%) which formed colourless plates, m.p. 199-201° (decomp.) (from glacial acetic acid-water), ν_{max} 3161 (NH), 3100-2500 br (NH,OH) and 1732, 1699 and 1663 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 10.6 (2H, bs, 2 x NH) (exch.), 8.48 (1H, dd, J = 8 and 2 Hz, ArH), 7.71 (1H, dd, J = 4 and 2 Hz, ArH), 7.46 (1H, dd, J = 8 and 4 Hz, ArH), 4.30 (2H, q, J = 7 Hz, CH_2), 4.21 (2H, q, J = 7 Hz, CH_2), 1.28 (3H, t, J = 7 Hz, CH_3) and 1.25 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the ethereal mother liquor gave no further material.

5-*N*-Ethoxycarbonylpyrimido[4,5-c]-1,5-napthyridine-2,4,6(1H,3H,5H)-trione (241)

A suspension of 1-ethoxycarbonyl-3-(4-ethoxycarbonyl-1,5-napthyridin-2(1H)-on-3-yl)urea (240) (2.4g; 0.007mol) in 2M aqueous sodium hydroxide (17.5ml) was stirred at room temperature for 0.5h.

The mixture was diluted with water (10.0ml) then acidified with glacial acetic acid and the precipitated solid was collected to afford 5-*N*-ethoxycarbonylpyrimido[4,5-c]-1,5-napthyridine-2,4,6(1H,3H,5H)-trione (241) (1.6g; 76%) which formed colourless, irregular crystals, m.p. 264-266° (decomp.) (from dimethylformamide), ν_{max} 3340 (NH), 3100-2500 br (NH,OH) and 1780, 1735 and 1685 (C=O) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 12.6 (1H, bs, NH or OH) (exch.), 8.55 (1H, dd, J = 4 and 2 Hz, ArH), 7.72 (1H, dd, J = 8 and 2 Hz, ArH), 7.46 (1H, dd, J = 8 and 4 Hz, ArH), 4.46 (2H, q, J = 7 Hz, CH_2) and 1.34 (3H, t, J = 7 Hz, CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 20.0ml) gave no material.

Pyrimido[4,5-c]-1,5-napthyridine-2,4,6(1H,3H,5H)-trione (239)

A suspension of 5-*N*-ethoxycarbonylpyrimido[4,5-c]-1,5-napthyridine-2,4,6(1H,3H,5H)-trione (241) (0.30g; 0.001mol) in 2M aqueous sodium hydroxide (5.0ml) was stirred and heated under reflux for 0.5h.

The mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to afford pyrimido[4,5-c]-1,5-napthyridine-2,4,6(1H,3H,5H)-trione (239) (0.23g; 100%) as a tan powder, m.p. >360°, ν_{max} 3100-2500 br (NH,OH) and 1722, 1703 and 1675 (C=O) cm^{-1}, $\delta_H(CF_3CO_2H)$ 8.48 (1H, d, J = 6 Hz, ArH), 8.28 (1H, d, J = 9 Hz, ArH) and 7.73 (1H, dd, J = 9 and 6 Hz, ArH).

The Attempted Reaction of Diethyl 2-Chloro-1,5-napthyridine-3,4-dicarboxylate (223) with Urea

A solution of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.31g: 0.001mol) and urea (0.060g; 0.001mol) in anhydrous dimethylformamide (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue treated with water (10.0ml) and the resulting mixture extracted with methylene chloride (3 x 10.0ml) to give a waxy, yellow solid which was washed with hexane to afford only unreacted diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.17g; 55%) as a yellow solid, m.p. 61-64°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the hexane mother liquor gave only a complex, yellow oil (0.08g) which was not further investigated.

The Attempted Reaction of Diethyl 2-Chloro-1,5-napthyridine-3,4-dicarboxylate (223) with Sodium Cyanamide

A mixture of diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.31g: 0.001mol) and sodium cyanamide (0.060g; 0.001mol) in anhydrous dimethylformamide (5.0ml) was stirred and heated at 100° (oil bath) with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated, the residue treated with water (5.0ml) and the resulting mixture extracted with methylene chloride (3 x 5.0ml) to give a yellow oil

which was triturated with hexane to afford only unreacted diethyl 2-chloro-1,5-napthyridine-3,4-dicarboxylate (223) (0.11g; 35%) as a yellow solid, m.p. 59-66°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the hexane mother liquor gave only a complex, orange gum (0.065g) which was not further investigated.

1-(3,4-Diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245)

(a) A solution of diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (0.29g; 0.001mol) in anhydrous dimethylformamide (2.5ml) was treated with a solution of ethoxycarbonyl isocyanate (0.12g; 0.001mol) in anhydrous dimethylformamide (2.5ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 17h.

Rotary evaporation of the mixture gave a yellow oil (0.25g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave only unreacted diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (0.15g; 51%) as a yellow solid, m.p. 137-145°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with hexane-ethyl acetate (7:3) afforded 1-(3,4-diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) (0.082g; 20%) which formed colourless, irregular crystals, m.p. 115-117° (from ethanol), ν_{max} 3272 and 3212 (NH) and 1744 and 1694 (C=O) cm^{-1}, δ_H ($CDCl_3$) 11.3 (1H, bs, NH) (exch.), 10.7 (1H, bs, NH) (exch.), 8.90 (1H, dd, J = 4 and 2 Hz, ArH), 8.14 (1H, dd, J = 9 and 2 Hz, ArH), 7.67 (1H, dd, J = 9 and 4 Hz, ArH), 4.55 (2H, q, J = 7 Hz, CH_2), 4.46 (2H, q, J = 7 Hz, CH_2), 4.31 (2H, q, J = 7 Hz, CH_2), 1.42 (3H, t, J = 7 Hz, CH_3), 1.40 (3H, t, J = 7 Hz, CH_3) and 1.35 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

(b) A solution of diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (0.29g; 0.001mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was treated with a solution of ethoxycarbonyl isocyanate (0.12g; 0.001mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the resulting solution was stirred and heated under reflux under a nitrogen atmosphere for 17h.

Rotary evaporation of the mixture gave a yellow gum (0.51g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:1) gave only unreacted diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (0.12g; 41%) as a yellow solid, m.p. 140-145°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with hexane-ethyl acetate (3:2) afforded 1-(3,4-diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) (0.057g; 14%) as a yellow solid, m.p. 118-120°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Elution with hexane-ethyl acetate (1:1) and then finally with methanol gave only a series of multicomponent oils and gums (total 0.13g) which were not further investigated.

(c) A solution of diethyl 2-amino-1,5-napthyridine-3,4-dicarboxylate (226) (0.29g; 0.001mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was treated with a solution of ethoxycarbonyl isocyanate (0.35g; 0.003mol) in anhydrous 1,2-dimethoxyethane (5.0ml) and the resulting solution was stirred and heated under reflux under a nitrogen atmosphere for 5h.

Rotary evaporation of the mixture gave a colourless gum (0.58g) which was crystallised from ethanol to afford 1-(3,4-diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) (0.15g; 37%) as a pale yellow solid, m.p. 113-115°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethanolic mother liquor afforded further 1-(3,4-diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) (0.25g; 62%) as a pale yellow gum identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

The Reaction of 1-(3,4-Diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) with Aqueous Sodium Hydroxide

A solution of 1-(3,4-diethoxycarbonyl-1,5-napthyridin-2-yl)-3-ethoxycarbonylurea (245) (0.68g; 0.0017mol) in 2M aqueous sodium hydroxide (5.0ml) was stirred at room temperature for 0.5h.

The mixture was acidified with glacial acetic acid then cooled to 5° (ice bath) and the resulting suspension was filtered to give a cream solid (0.17g) which left a residue on roasting. A suspension of this salt in 2M aqueous hydrochloric acid was stirred at room temperature for 15min then filtered to afford a colourless solid which was combined with a second crop obtained by acidification of the original alkaline mother liquor with 2M aqueous hydrochloric acid followed by filtration to give a product tentatively identified as diethyl pyrimido[4,5-b]-1,5-napthyridine-2,4(1H,3H)-dione-3,5-dicarboxylate monohydrate (246), (total 0.34g; 53%) which formed colourless needles, m.p. 168-170° (decomp.) (from ethanol), ν_{max} 3600-2100 br (NH, OH) and 1784, 1734, 1697 and 1670 (C=O) cm^{-1}, $\delta_H[(CD_3)_2\dot{S}=O]$ 11.1 (2H, bs, NH and OH) (exch.), 8.97 (1H, dd, J = 4 and 2 Hz, ArH), 8.30 (1H, dd, J = 9 and 2 Hz, ArH), 7.87 (1H, dd, J = 9 and 4 Hz, ArH), 4.42 (2H, q, J = 7 Hz, CH_2), 4.23 (2H, q, J = 7 Hz, CH_2), 1.33 (3H, t, J = 7 Hz, CH_3) and 1.28 (3H, t, J = 7 Hz, CH_3).

N-(2-Ethoxalylpyrid-3-yl)hydrazones (247a-c)

A solution of ethyl 2-(3-aminopyrid-2-yl)-2-oxoethanoate (188) (1.9g; 0.01mol) in 2M aqueous nitric acid (20.0ml) was cooled to 0-5° (ice bath) and treated dropwise with a solution of of sodium nitrite (0.75g; 0.011mol) in water (5.0ml) at

such a rate that the reaction temperature did not exceed 5°. The resulting yellow solution was stirred at 0-5° (ice bath) for 15 min then added dropwise to a stirred, pre-cooled [0-5° (ice bath)] solution of the appropriate ketone (0.01mol) and sodium acetate (6.0g) in ethanol (25.0ml) and water (25.0ml) and the resulting mixture was stirred and allowed to warm to room temperature over 2h then worked up as described for the individual reactions below.

(i) Ethyl 2,3-Dioxobutanoate 2-*N*-(2-Ethoxalylpyrid-3-yl)hydrazone (247a)

The mixture from ethyl 3-oxobutanoate was filtered to give a yellow solid which was washed with water (2.5ml) then with ethanol (2.5ml) to afford ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (2.2g; 66%) which formed pale yellow needles, m.p. 88-89° (from hexane-ethyl acetate), ν_{max} 3220-3120 br (NH) and 1740, 1700 and 1680 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ 13.7 (1H, bs, NH) (exch.), 8.41 (1H, dd, J = 4 and 1 Hz, ArH), 8.24 (1H, dd, J = 9 and 1 Hz, ArH), 7.53 (1H, dd, J = 9 and 4 Hz, ArH), 4.46 (4H, q, J = 7 Hz, 2 x CH_2), 2.50 (3H, s, CH_3), 1.40 (3H, t, J = 7 Hz, CH_3) and 1.38 (3H, t, J = 7 Hz, CH_3).

Extraction of the aqueous mother liquor with methylene chloride (3 x 25.0ml) gave only a multicomponent brown oil (0.80g) which was not further investigated.

(ii) Ethyl 2,3-Dioxo-3-phenylpropanoate 2-*N*-(2-Ethoxalylpyrid-3-yl)hydrazone (247b)

The mixture from ethyl 3-oxo-3-phenylpropanoate was rotary evaporated and the resisue treated with water and the resulting solution extracted with methylene chloride to give an orange oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded ethyl 2,3-dioxo-3-phenylpropanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247b) (68%) which formed pale yellow plates, m.p. 99-101° (from ethanol), ν_{max} 3148 (NH) and 1744, 1697, 1666 and 1655 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ 14.0 (1H, bs, NH) (exch.), 8.34 (1H, dd, J = 4 and 1 Hz, ArH), 8.03-7.85 (3H, m, 3 x ArH), 7.62-7.31 (4H, m, 4 x ArH), 4.46 (2H,

q, J = 7 Hz, CH_2), 4.42 (2H, q, J = 7 Hz, CH_2), 1.38 (3H, t, J = 7 Hz, CH_3) and 1.31 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

(iii) Pentane-2,3,4-trione 2-*N*-(2-Ethoxalylpyrid-3-yl)hydrazone (247c)

The mixture from pentane-2,4-dione was filtered to give a yellow solid which was washed with water then with ethanol to afford pentane-2,3,4-trione 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247c) (70%) which formed yellow plates, m.p. 124-126° (from ethanol), ν_{max} 3600-3300 br (NH) and 1740, 1690 and 1675 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ 15.2 (1H, bs, NH) (exch.), 8.44 (1H, dd, J = 4 and 1 Hz, ArH), 8.32 (1H, ddd, J = 9, 1 and 0.4 Hz, ArH), 7.55 (1H, ddd, J = 9, 4 and 0.7 Hz, ArH), 4.44 (2H, q, J = 7 Hz, CH_2), 2.59 (3H, s, CH_3), 2.48 (3H, s, CH_3) and 1.37 (3H, t, J = 7 Hz, CH_3).

Extraction of the aqueous mother liquor with methylene chloride gave only a small amount of a multicomponent brown oil which was not further investigated.

Attempted Cyclisation Reactions of Ethyl 2,3-Dioxobutanoate 2-*N*-(2-Ethoxalylpyrid-3-yl)hydrazone (247a)

(a) A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.34g; 0.001mol) in anhydrous ethanol (5.0ml) was treated with a solution of sodium (0.092g; 0.008g.atom) in anhydrous ethanol (5.0ml) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated and the residue was treated with water (10.0ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride (3 x 10.0ml) to give no material.

The aqueous phase was rotary evaporated and the residue extracted with boiling ethyl acetate (2 x 50.0ml) to give no material.

(b) A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.34g; 0.001mol) in anhydrous ethanol (5.0ml) was treated with piperidine (0.17g; 0.002mol) and the resulting red solution was stirred at room temperature with exclusion of atmospheric moisture for 24h.

Rotary evaporation of the mixture gave only an inractable, multicomponent red gum (0.53g) which was not further investigated.

Diethyl Pyrido[3,2-c]pyridazine-3,4-dicarboxylate (249a)

(a) A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.34g; 0.001mol) in anhydrous ethanol (5.0ml) was treated with piperidine (0.085g; 0.001mol) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was rotary evaporated to give a brown solid (0.29g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) afforded diethyl pyrido [3,2-c]pyridazine-3,4-dicarboxylate (249a) (0.075g; 27%) which formed yellow plates, m.p. 143-146° (from ethanol), ν_{max} 1743 and 1723 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.30 (1H, dd, J = 4 and 2 Hz, ArH), 8.97 (1H, dd, J = 9 and 2 Hz, ArH), 7.92 (1H, dd, J = 9 and 4 Hz, ArH), 4.64 (2H, q, J = 7 Hz, CH_2), 4.62 (2H, q, J = 7 Hz, CH_2), 1.51 (3H, t, J = 7 Hz, CH_3) and 1.46 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a complex brown solid (0.13g), m.p. 184-210° (decomp.), from which no identifiable material could be obtained.

(b) A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.34g; 0.001mol) in anhydrous ethanol (5.0ml) was treated with

triethylamine (0.10g; 0.001mol) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 18h.

The mixture was rotary evaporated to give a brown gum (0.38g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) gave a multicomponent green gum (0.03g) which was not further investigated.

Elution with hexane-ethyl acetate (2:3) afforded diethyl pyrido [3,2-c]pyridazine-3,4-dicarboxylate (249a) (0.11g; 40%) as a yellow solid, m.p. 132-135°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only a complex brown solid (0.16g), m.p. 110-260° (decomp.), from which no identifiable material could be obtained.

(c) A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.34g; 0.001mol) in anhydrous ethanol (5.0ml) was treated with triethylamine (0.20g; 0.002mol) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

The mixture was rotary evaporated to give a brown gum (0.35g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent green oil (0.22g) which was not further investigated.

Elution with hexane-ethyl acetate (3:2) afforded diethyl pyrido [3,2-c]pyridazine-3,4-dicarboxylate (249a) (0.060g; 22%) as a yellow solid, m.p. 138-142°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only a complex brown glass (0.10g), m.p. 95-130° (decomp.), which was not further investigated.

Dimethyl Pyrido[3,2-c]pyridazine-3,4-dicarboxylate (249b)

A solution of ethyl 2,3-dioxobutanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247a) (0.67g; 0.002mol) in anhydrous methanol (10.0ml) was treated with 40% w/v methanolic benzyl triethylammonium hydroxide solution (1.0ml) and the resulting red solution was stirred at room temperature with exclusion of atmospheric moisture for 24h.

The mixture was rotary evaporated and the residue was treated with water (5.0ml). The resulting solution was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride (3 x 10.0ml) to give a red gum (0.44g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) afforded dimethyl pyrido [3,2-c]pyridazine-3,4-dicarboxylate (249b) (0.20g; 41%) which formed pale yellow needles, m.p. 133-134° (from ethanol), ν_{max} 1750 and 1730 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.28 (1H, dd, J = 4 and 2 Hz, ArH), 8.96 (1H, dd, J = 9 and 2 Hz, ArH), 7.90 (1H, dd, J = 9 and 4 Hz, ArH) and 4.13 (6H, s, 2 x CH_3).

Final elution with methanol gave only a complex brown solid (0.12g), m.p. 153-310° (decomp.), from which no identifiable material could be obtained.

The Base-Catalysed Cyclisation Reaction of Ethyl 2,3-Dioxo-3-phenylpropanoate 2-*N*-(2-Ethoxalylpyrid-3-yl)hydrazone (247b)

A solution of ethyl 2,3-dioxo-3-phenylpropanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247b) (1.2g; 0.003mol) in anhydrous ethanol (15.0ml) was treated with triethylamine (0.30g; 0.003mol) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 24h.

The mixture was rotary evaporated to give a brown oil (1.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2,3-dioxo-3-phenylpropanoate 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247b) (0.75g; 63%) as a yellow solid, m.p. 97-99°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with hexane-ethyl acetate (3:2) afforded diethyl pyrido [3,2-c]pyridazine-3,4-dicarboxylate (249a) (0.10g; 12%) as a yellow solid, m.p. 124-128°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave only a complex brown gum (0.10g) which was not further investigated.

3-Acetylpyrido[3,2-c]pyridazine-4-carboxylate (249c)

A solution of pentane-2,3,4-trione 2-*N*-(2-ethoxalylpyrid-3-yl)hydrazone (247c) (1.5g; 0.005mol) in anhydrous ethanol (25.0ml) was treated with triethylamine (0.51g; 0.005mol) and the resulting red solution was stirred and heated under reflux with exclusion of atmospheric moisture for 17h.

The mixture was rotary evaporated to give a dark brown gum (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave a multicomponent brown oil (0.04g) which was not further investigated.

Further elution with hexane-ethyl acetate (7:3) afforded 3-acetylpyrido [3,2-c]pyridazine-4-carboxylate (249c) which formed yellow prisms, m.p. 95-96° (from ethanol), ν_{max} 1740 and 1710 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.28 (1H, dd, J = 4 and 2 Hz, ArH), 8.92 (1H, dd, J = 9 and 2 Hz, ArH), 7.89 (1H, dd, J = 9 and 4 Hz, ArH), 4.65 (2H, q, J = 7 Hz, CH_2), 3.05 (3H, s, CH_3) and 1.45 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave only a complex brown gum (0.80g) which was not further investigated.

Table 14 : Elemental Analyses and Mass Spectroscopic Data

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)$ [a]
(93) ($C_6H_6N_2O_2.1/2H_2O$)	48.6	4.5	18.8	(139)	49.0	4.8	19.0	138
(102a) ($C_{12}H_{14}N_2O_6$)	50.9	4.9	9.8	(283)	51.1	5.0	9.9	282
(102b) ($C_{10}H_{10}N_2O_6$)	47.2	4.0	10.9	(255)	47.2	3.9	11.0	254
(102c) ($C_{16}H_{22}N_2O_6$)	56.9	6.6	8.4	(339)	56.8	6.5	8.3	338
(102d) ($C_{22}H_{18}N_2O_6$)	65.0	4.5	7.0	(407)	65.0	4.4	6.9	406
(103a) ($C_9H_8N_2O_3$)	56.2	4.2	14.6	192	56.2	4.2	14.6	192
(103b) ($C_8H_6N_2O_3$)	54.1	3.6	15.6	178	53.9	3.4	15.7	178
(103c) ($C_{11}H_{12}N_2O_3$)	60.0	5.7	12.5	220	60.0	5.5	12.7	220
(103d) ($C_{14}H_{10}N_2O_3$)	65.9	4.1	11.2	254	66.1	3.9	11.0	254
(103e) ($C_7H_3N_2O_3Na.H_2O$)	41.2	2.5	13.9	-	41.2	2.5	13.7	209
(103f) ($C_7H_4N_2O_3$)	52.0	2.5	17.1	(165.0300)	51.2	2.4	17.1	(165.0300)
(104a) ($C_9H_{10}N_2O_4$)	51.2	5.0	12.4	(211.0707)	51.4	4.8	13.3	(211.0719)
(104c) ($C_{11}H_{14}N_2O_4$)	55.3	5.9	11.8	(239)	55.5	5.9	11.8	238
(105a) ($C_{11}H_{12}N_2O_5$)	51.8	4.9	12.5	(253.0826)	52.4	4.8	11.1	(253.0824)
(105b) ($C_{16}H_{14}N_2O_5$)	61.2	5.0	8.4	314.0894	61.1	4.5	8.9	314.0903
(105d) ($C_{10}H_9N_3O_4$)	51.2	3.8	17.9	(236)	51.1	3.8	17.9	235
(105e) ($C_{15}H_{14}N_2O_6S$)	51.7	4.1	8.0	(351)	51.4	4.0	8.0	350
(106a) ($C_8H_6N_2O_2$)	-	-	-	(163.0508)	-	-	-	(163.0507)
(106b) ($C_{13}H_8N_2O_2$)	69.4	3.9	12.4	224	69.6	3.6	12.5	224
(106d) ($C_7H_3N_3O$)	57.8	2.2	28.9	145	57.9	2.0	29.0	145

Table 14 ; Elemental Analyses and Mass Spectroscopic Data (cont.)

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)$ [a]
(111) ($C_{12}H_{14}N_2O_6$)	50.7	5.0	10.0	(283)	51.1	5.0	9.9	282
(112) ($C_{12}H_{14}N_2O_6$)	56.4	4.2	14.7	192	56.3	4.2	14.6	192
(113) ($C_9H_{10}N_2O_4$)	51.5	4.7	12.6	(211.0720)	51.4	4.8	13.3	(211.0719)
(118) ($C_{17}H_{16}N_2O_6$)	-	-	-	(345.1082)	-	-	-	(345.1087)
(121) ($C_{12}H_{14}N_2O_6$)	50.8	4.9	9.9	282	51.1	5.0	9.9	282
(122) ($C_9H_{10}N_2O_4$)	51.4	4.9	13.3	210	51.4	4.8	13.3	210
(125) ($C_7H_6N_2O_3$)	-	-	-	(167.0457)	-	-	-	(167.0457)
(128) ($C_{12}H_{14}N_2O_7$)	48.2	4.7	9.4	(299)	48.3	4.7	9.4	298
(129) ($C_{13}H_{16}N_2O_7$)	50.3	5.3	9.2	312	50.0	5.1	9.0	312
(134) ($C_{10}H_8N_4O_5$)	45.5	3.0	21.3	(265)	45.5	3.0	21.2	264
(137) ($C_{11}H_{13}N_5O_5$)	44.6	4.5	23.3	295	44.7	4.4	23.7	295
(138) ($C_{10}H_{13}N_3O_3$)	53.9	5.8	18.9	223	53.8	5.8	18.8	223
(139a) ($C_{10}H_{10}N_2O_7$)	44.4	3.7	10.2	(271)	44.4	3.7	10.4	270
(139b) ($C_{16}H_{22}N_2O_7$)	53.5	6.1	8.7	(355.1505)	54.2	6.2	7.9	(355.1505)
(146) ($C_{13}H_{16}N_2O_6$)	52.6	5.5	9.6	296	52.7	5.4	9.5	296
(149) ($C_{12}H_{14}N_2O_7$)	48.1	5.0	9.4	(299)	48.3	4.7	9.4	298
(150) ($C_{12}H_{14}N_2O_8$)	45.9	4.5	8.5	314	45.9	4.5	8.9	314
(151) ($C_{12}H_{14}N_2O_8$)	45.6	4.3	8.9	314	45.9	4.5	8.9	314
(152) ($C_{12}H_{14}N_2O_7$)	48.2	4.7	9.3	(299)	48.3	4.7	9.4	298
(156) ($C_6H_4N_2O_4$)	42.9	2.5	16.8	(169)	42.9	2.4	16.7	168

Table 14 ; Elemental Analyses and Mass Spectroscopic Data (cont.)

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)^+$ [a]
(158) ($C_9H_{10}N_2O_5$)	47.9	4.8	12.0	226.0579	47.8	4.4	12.4	226.0590
(160) ($C_9H_9N_3O_5$)	45.5	3.8	17.4	239	45.2	3.8	17.6	239
(162) ($C_9H_8N_2O_5$)	47.9	3.6	12.4	(255)	48.2	3.6	12.5	254
(164) ($C_{11}H_{11}N_3O_4$)	53.3	4.7	16.8	249	53.0	4.4	16.9	249
(171) ($C_8H_4N_4O_2$)	51.4	2.1	29.7	188	51.1	2.1	29.8	188
(172) ($C_9H_6N_4O_2$)	53.5	3.1	27.8	202	53.5	3.0	27.7	202
(176) ($C_6H_5N_3O_3$)	43.1	3.0	24.8	(168)	43.1	3.0	25.1	167
(177) ($C_8H_8N_2O_4$)	-	-	-	(197.0553)	49.0	4.1	14.3	(197.0562)
(178) ($C_8H_4N_4O_2$)	51.4	2.2	29.8	188	51.1	2.1	29.8	188
(180a) ($C_9H_8N_4O_3$)	49.2	3.6	25.7	220	49.1	3.6	25.5	220
(180b) ($C_{14}H_{10}N_4O_3$)	59.5	3.6	19.9	282	59.6	3.6	19.9	282
(180c) ($C_{11}H_{13}N_3O_5$)	49.2	5.1	15.7	(268)	49.4	4.9	15.7	267
(181a) ($C_8H_7N_3O_3$)	49.9	3.6	21.9	(194)	49.7	3.6	21.8	193
(181b) ($C_{13}H_9N_3O_3$)	60.9	3.6	16.3	255	61.2	3.5	16.5	255
(182) ($C_{10}H_{11}N_3O_4$)	50.8	3.9	17.8	235	51.1	3.8	17.9	235
(184) ($C_8H_7N_3O_2$)	53.9	4.1	23.2	177	54.2	4.0	23.7	177
(187) ($C_9H_{12}N_2O_3$)	55.5	5.9	14.5	196	55.1	6.1	14.3	196
(188) ($C_9H_{10}N_2O_3$)	55.0	5.2	14.5	194.0699	55.7	5.2	14.4	194.0691
(189) ($C_9H_{10}N_2O_3$)	55.3	4.9	14.3	194	55.7	5.2	14.4	194
(190) ($C_{15}H_{18}N_2O_6$)	55.7	5.3	8.6	(323)	55.9	5.6	8.7	322

Table 14 ; Elemental Analyses and Mass Spectroscopic Data (cont.)

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)$ [a]
(191a) ($C_{13}H_{12}N_2O_4$)	60.4	4.6	10.9	260	60.0	4.6	10.8	260
(191b) ($C_{18}H_{14}N_2O_4$)	67.0	4.3	8.6	322	67.1	4.3	8.7	322
(191c) ($C_{15}H_{14}N_2O_6$)	56.5	4.5	8.8	(319)	56.6	4.4	8.8	318
(192a) ($C_{11}H_8N_4O_2$)	56.9	3.7	23.4	228.0650	57.9	3.5	24.6	228.0647
(192b) ($C_{16}H_{10}N_4O_2$)	65.2	3.6	19.2	(291.0882)	66.2	3.5	19.3	(291.0882)
(192c) ($C_{13}H_{10}N_4O_4$)	52.8	3.7	18.1	286.0692	54.5	3.5	19.6	286.0702
(195) ($C_{14}H_{14}N_2O_5$)	58.0	4.8	9.7	290	57.9	4.8	9.7	290
(196) ($C_{10}H_6N_4O_3$)	42.0	3.4	24.0	(231.0518)	52.2	2.6	24.3	(231.0518)
(197) ($C_{21}H_{18}N_4O_7$)	56.5	4.1	12.4	(439.1253)	57.5	4.1	12.8	(439.1254)
(199) ($C_{17}H_{16}N_2O_4$)	65.3	5.4	9.0	(313)	65.4	5.1	9.0	312
(202) ($C_{11}H_{11}ClN_2O_4$)	48.7	4.4	10.1	(273), (271)	48.8	4.1	10.4	272, 270
(205) ($C_{17}H_{14}N_2O_5S$)	56.6	3.9	7.7	(359)	57.0	3.9	7.8	358
(206) ($C_{16}H_{14}ClN_3O_3$)	58.2	4.3	12.6	296 [$(M-Cl)^+$]	57.9	4.2	12.7	333, 331
(207) ($C_{11}H_{11}N_3O_3$)	56.7	4.8	18.0	233	56.7	4.7	18.0	233
(208) ($C_7H_5N_3O$)	57.1	3.5	28.3	147	57.1	3.4	28.6	147
(209) ($C_8H_{10}N_2O_2$)	57.8	6.2	16.8	166	57.8	6.0	16.9	166
(210a) ($C_{12}H_{11}N_3O_4$)	-	-	-	(262.0828)	-	-	-	(262.0828)
(210b) ($C_{11}H_{12}N_2O_5$)	52.6	4.7	10.6	252.0746	52.4	4.8	11.1	252.0746
(211) ($C_{12}H_9N_3O_3$)	59.5	4.0	17.3	243	59.3	3.7	17.3	243
(212) ($C_{10}H_7N_5O_2$)	48.5	3.7	28.8	229.0581	52.4	3.1	30.6	229.0560

Table 14 ; Elemental Analyses and Mass Spectroscopic Data (cont.)

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)$ [a]
(213) ($C_9H_6ClN_3O_2$)	48.2	2.7	17.3	225.0125, 223.0139	48.3	2.7	18.8	225.0120, 223.0149
(215) ($C_7H_5N_3O_2$)	51.4	3.2	25.6	163	51.5	3.1	25.8	163
(216) ($C_7H_9N_3O_2$)	50.2	5.5	24.8	167	50.3	5.4	25.1	167
(217) ($C_7H_7N_3O_2$)	50.6	4.5	25.3	165	50.9	4.2	25.5	165
(219) ($C_9H_8ClN_3O_3$)	44.5	3.5	17.0	(244), (242)	44.7	3.3	17.4	243, 241
(220) ($C_9H_{10}N_2O_3$)	51.8	4.8	15.0	194.0691	55.7	5.1	14.4	194.0691
(221) ($C_{13}H_{12}N_2O_4$)	60.2	4.7	10.6	260	60.0	4.6	10.8	260
(222) ($C_{14}H_{14}N_2O_5$)	57.7	4.8	9.34	(291)	57.9	4.8	9.66	290
(222).HCl ($C_{14}H_{14}ClN_2O_5$)	51.9	4.7	8.5	291 [$(M-Cl^-)$]	51.5	4.6	8.6	328, 326
(223) ($C_{14}H_{13}ClN_2O_4$)	54.5	4.2	9.0	310, 308	54.5	4.2	9.1	310, 308
(224) ($C_{21}H_{21}N_3O_4$)	66.3	5.4	11.1	(380)	66.5	5.5	11.1	379
(225) ($C_{20}H_8N_2O_6S$)	57.9	4.6	6.8	(415)	58.0	4.5	6.8	414
(226) ($C_{14}H_{15}N_3O_4$)	57.8	5.3	14.4	289	58.1	5.2	14.5	289
(227) ($C_{14}H_{13}N_5O_4$)	53.5	4.4	22.3	(316)	53.3	4.1	22.2	315
(228) ($C_{32}H_{28}N_3O_4P$)	69.7	5.4	7.5	549	69.9	5.1	7.6	549
(229) ($C_{14}H_{14}N_2O_7$)	52.4	4.3	8.5	(323)	52.2	4.3	8.7	322
(230) ($C_{14}H_{14}N_2O_6$)	55.0	4.5	9.2	(307)	54.9	4.6	9.1	306
(231) ($C_{14}H_{16}N_2O_8$)	49.5	5.06	8.3	(341)	49.4	4.71	8.2	340
(232) ($C_6H_6N_2O_3$)	55.2	4.6	7.1	(391)	55.4	4.6	7.2	390
(235) ($C_{14}H_{14}N_2O_6$)	54.6	4.6	8.9	306	54.9	4.6	9.1	306

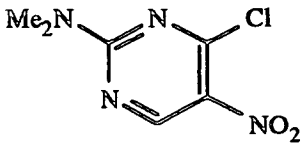
Table 14 ; Elemental Analyses and Mass Spectroscopic Data (cont.)

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)$ [a]
(239) ($C_{10}H_6N_4O_3$)	40.2	3.2	18.0	(231.0518)	52.2	2.6	24.3	(231.0518)
(240) ($C_{15}H_{16}N_4O_6$)	51.3	4.5	16.3	348	51.7	4.6	16.1	348
(241) ($C_{12}H_{12}N_4O_4$)	51.6	3.4	18.4	(303)	51.7	3.3	18.5	302
(245) ($C_{18}H_{20}N_4O_7$)	53.7	5.0	13.9	404	53.5	5.0	13.9	404
(246) ($C_{16}H_{14}N_4O_6.1/2H_2O$)	51.1	4.3	14.9	358	50.3	4.6	14.5	358
(247a) ($C_{15}H_{17}N_3O_6$)	53.5	5.2	12.3	335	53.7	5.1	12.5	335
(247b) ($C_{20}H_{19}N_3O_6$)	60.2	4.9	10.4	397	60.5	4.8	10.6	397
(247c) ($C_{14}H_{15}N_3O_5$)	55.0	5.1	13.9	305	55.1	4.9	13.8	305
(249a) ($C_{13}H_{13}N_3O_4$)	56.7	4.8	15.3	(276)	56.7	4.7	15.3	275
(249b) ($C_{11}H_9N_3O_4$)	53.5	3.9	16.7	247	53.4	3.6	17.0	247
(249c) ($C_{12}H_{11}N_3O_3$)	58.9	4.6	17.2	245	58.8	4.5	17.1	245

a, molecular ions detected by Electron Impact Mass Spectroscopy or, for values in parentheses, molecular ions detected by Fast Atom Bombardment Mass Spectroscopy.

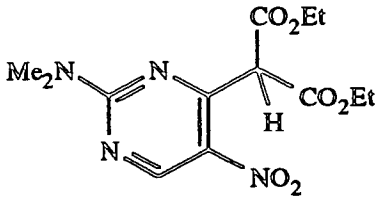
Chapter 3

Studies on the Synthesis and Reactivity of Isoxazolo[3,4-d]pyrimidine Derivatives



(252)

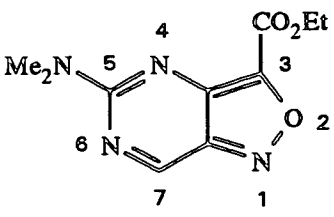
(i)



(253)

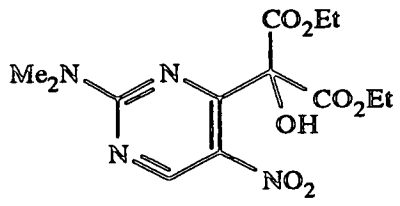
(ii) or (iii)

(iv)



(254)

(v)



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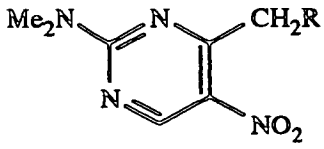


(256) R

a ; CO_2Et

b ; H

(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100°.

(ii) pyridine, reflux.

(iii) xylene, mol. sieves 5A, reflux.

(iv) 30% H_2O_2 aqu., 1M NaOH aqu., room temp.

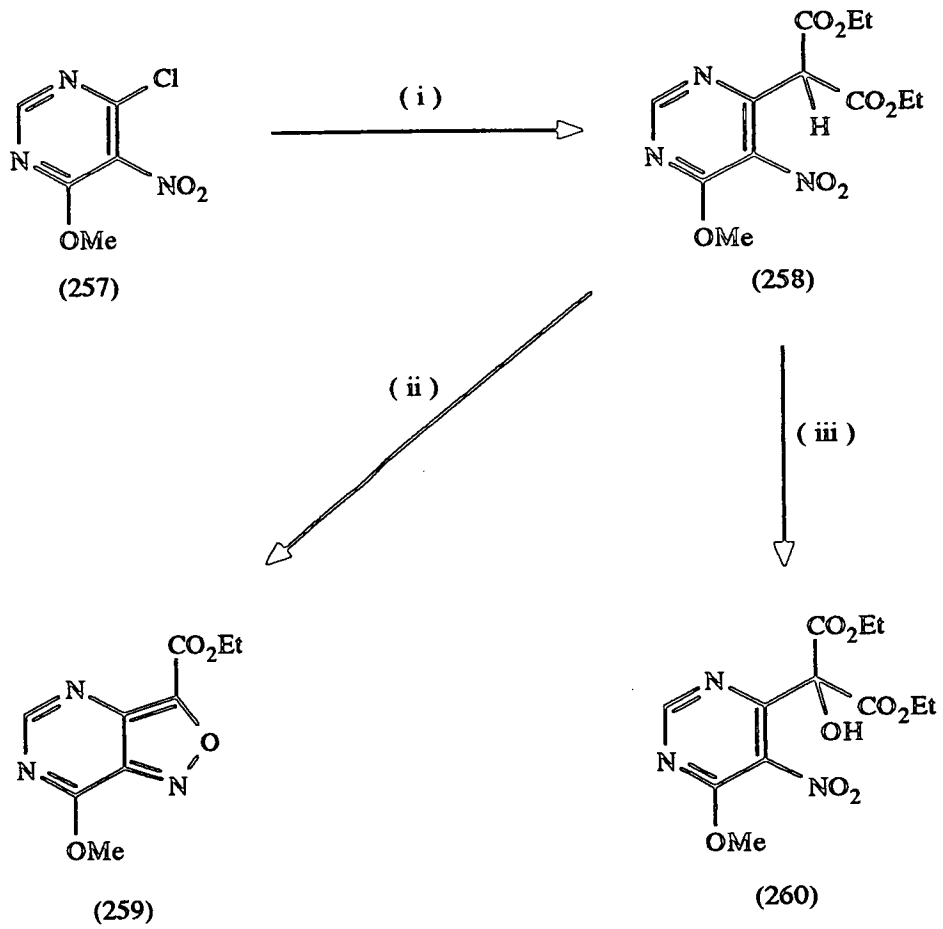
(v) pyridine, H_2O, reflux.

Scheme 76

3.1 : Studies on the Synthesis and Reactivity of Isoxazolo[3,4-d]pyrimidine Derivatives

In light of the successful synthesis and exploitation of the novel isoxazolopyridine derivatives as synthetic intermediates discussed in Chapter 2 of this thesis it was considered of interest to attempt to extend the methodology thereby developed to the synthesis of some novel isoxazolo[3,4d]pyrimidine derivatives. This was undertaken not only to investigate the generality of the new fused 3,4-isoxazole synthesis currently under investigation but also with a view to using the isoxazolopyrimidines so derived as precursors for other fused pyrimidines. The starting materials needed for the synthesis of the required isoxazolopyrimidines are *ortho*-halogenonitro pyrimidines and, as for the three pyrimidine derivatives which were studied and are discussed in this chapter, many such synthetic intermediates are readily available through literature procedures. Initially it was decided to investigate the synthesis and reactivity towards thermal cyclisation (Scheme76) of the dimethylaminonitropyrimidinylmalonate derivative (253).This substrate was readily synthesised in high yield by the reaction of the known[128] chloronitropyrimidine derivative (252) with the anion of diethyl malonate.

The pyrolysis reactions of the pyrimidine derivative (253) were then investigated. However this compound was unchanged after prolonged heating under reflux in either toluene or xylene solution whereas heating (253) under reflux in the higher boiling solvent diglyme resulted only in the production of an intractable mixture of products. However by heating a pyridine solution of (253) under prolonged reflux a low yield (27%) of a bright orange, crystalline solid was isolated whose elemental analysis and spectroscopic properties showed it to be the desired isoxazolo[4,3-d]pyrimidine derivative (254). This is the first example of this heterocyclic ring system which has been reported to date.



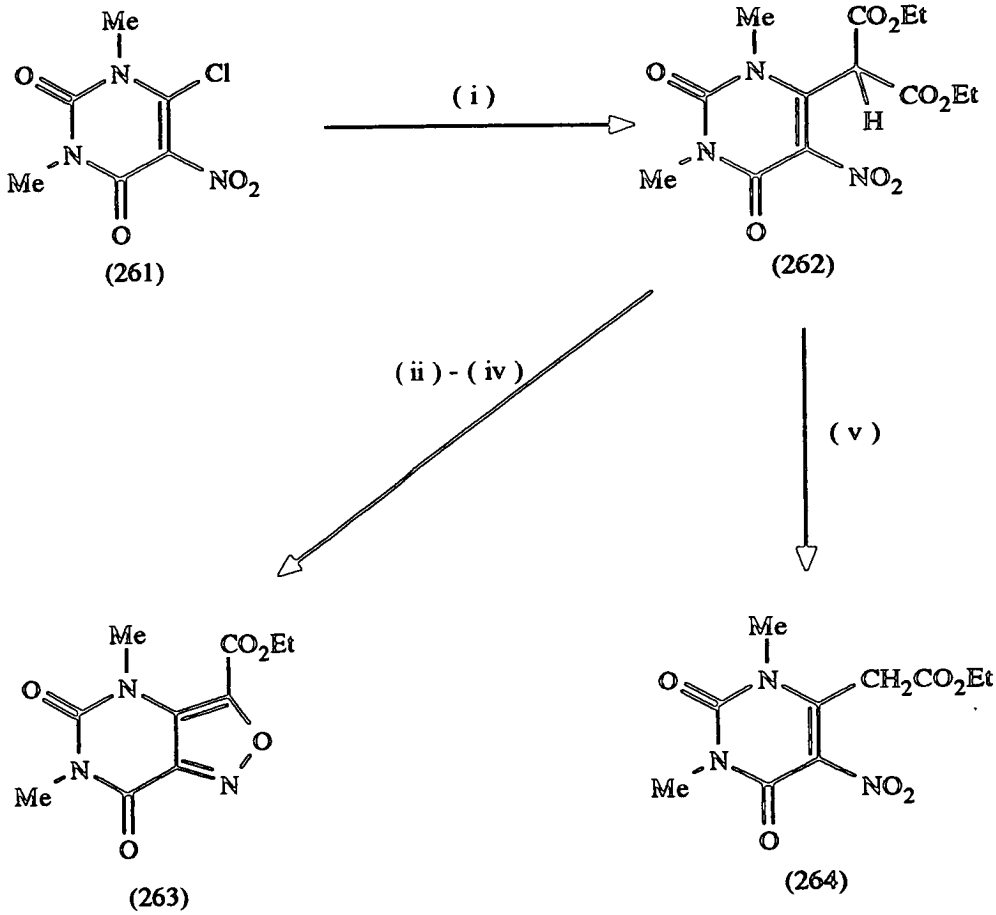
(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100°.
(ii) xylene, mol. sieves 5A, reflux.
(iii) 30% H_2O_2 aqu., AcOH, 50°.

Scheme 77

As an aside, the reaction of the nitropyrimidinylmalonate (253) in refluxing aqueous pyridine solution was also examined. After 24h under these conditions (253) afforded only low yields of the nitropyrimidinylacetate (256a) (29%) and the methylpyrimidine derivative (256b) (8%) together with some unreacted starting material. These conditions had been previously employed in the high yielding synthesis of ethyl 2-(3-nitropyrid-2-yl)acetate (104a) from diethyl 2-(3-nitropyrid-2-yl)propanedioate (102a) (see Chapter 2, Section 2.2) but proved to be less efficient when used to synthesise the analogous pyrimidine derivative (256a).

As was demonstrated in the course of the studies discussed in the previous chapter of this thesis, the removal of ethanol from the reaction mixture is crucial for the efficient pyrolysis of diethyl nitroarylmalonate derivatives such as (253). With this in mind a xylene solution of (253) was heated under reflux with removal of any ethanol produced by distillation through a vigreux column and this did indeed produce a moderate yield (41%) of the desired isoxazolopyrimidine (254). Further, it was pleasing to find that by heating a xylene solution of (253) under reflux using molecular sieves to remove any ethanol by-product a good yield of the anticipated isoxazolopyrimidine (254) (79%) was obtained.

With the efficient pyrolysis of the nitropyrimidinylmalonate (253) having been demonstrated it was next decided to study the pyrolysis of a second *ortho*-nitropyrimidinylmalonate derivative. To this end (Scheme 77) 4-chloro-6-methoxy-5-nitropyrimidine (257) was prepared according to a literature method[129] and then was condensed with the anion of diethyl malonate to afford the nitropyrimidinylmalonate derivative (258) in good yield (69%). The pyrolysis of (258) was performed in refluxing xylene solution with provision made for the removal of ethanol using molecular sieves and it was gratifying to find that these conditions did indeed produce the desired isoxazolopyrimidine (259) in a respectable 67% yield.

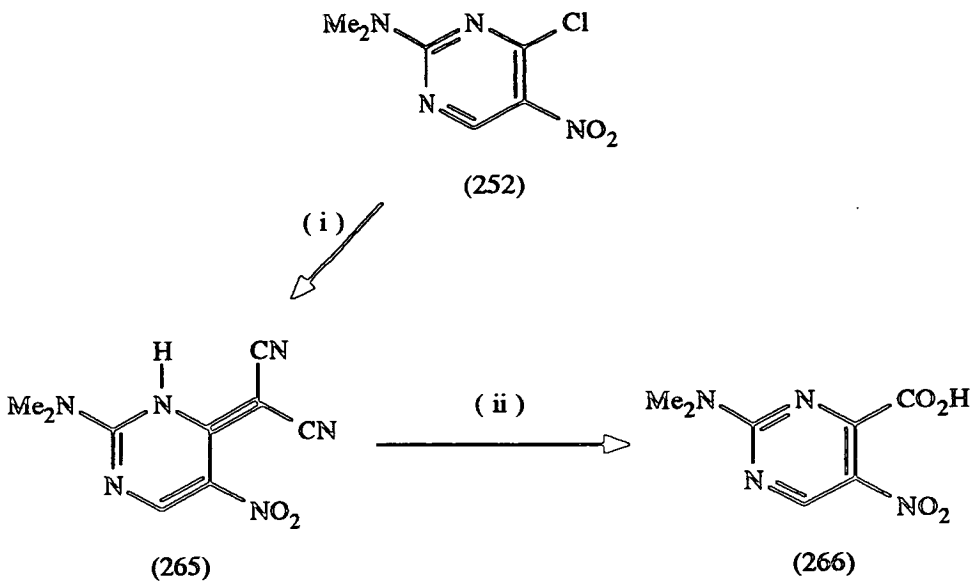


(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100°.
(ii) xylene, mol. sieves 5A, reflux.
(iii) toluene, mol. sieves 5A, reflux.
(iv) pyridine, reflux.
(v) pyridine, H_2O, reflux.

Scheme 78

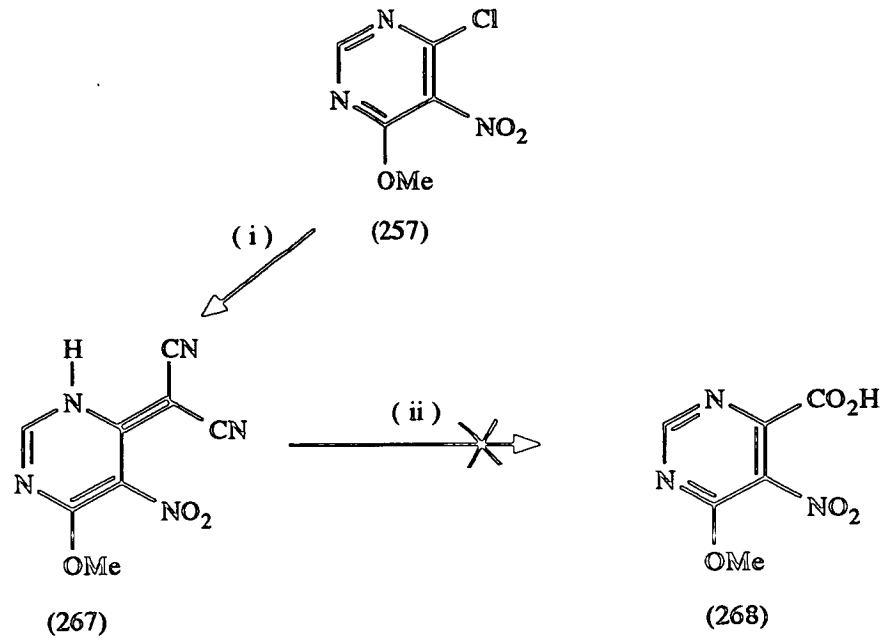
As a further assessment of the generality of the isoxazolopyrimidine synthesis, the pyrolysis (Scheme 78) of the nitrouracilmalonate derivative (262) was next examined. This compound was readily prepared in 70% yield by reaction of the known[130] *ortho*-chloronitropyrimidine derivative (261) with the anion of diethyl malonate. The pyrolysis of the pyrimidine derivative (262) in refluxing xylene solution using molecular sieves to remove the ethanol by-product proved to be very rapid with all of the starting material being consumed after 1h. Unfortunately a complex mixture was produced which, after flash-chromatography over silica, yielded only a small amount of the expected isoxazolouracil derivative (263) (8%) along with some of the nitrouracilacetate (264) (14%). This latter compound could also be prepared in near quantitative yield by the pyrolysis of (262) in refluxing aqueous pyridine solution, a reaction which also proved to be exceptionally rapid being complete after only 15 min. Since the pyrolyses of the nitrouracilmalonate (262) in xylene and aqueous pyridine were so rapid this prompted the investigation of the pyrolysis of the diester (262) in refluxing toluene solution again employing molecular sieves to remove the ethanol by-product. This was undertaken since the pyrolysis of the diester (262) in refluxing toluene alone gave after 2h only unreacted starting material and after 24h resulted in the isolation of only an intractable mixture. Under the molecular sieve mediated conditions all the starting material was consumed after only 5h but only a low yield (14%) of the desired isoxazolouracil derivative (263) was obtained together with the unwanted monoester derivative (264) (39%). The pyrolysis of the diester (262) in refluxing pyridine solution similarly afforded a low yield (17%) of the isoxazolouracil derivative (263) together with an inseparable, complex mixture of other products.

The reason for the difference in the thermal behaviour of the uracilmalonate derivative (262) and the two pyrimidinylmalonates [(253) and (258)] is not fully understood at present. The fact that the uracilmalonate (262) has considerably less aromatic character than the other two pyrimidinylmalonate derivatives may be an



(i) $CH_2(CN)_2$, NaH, DMF, room temp.
(ii) 30% H_2O_2 aqu., 1M NaOH aqu., room temp.

Scheme 79



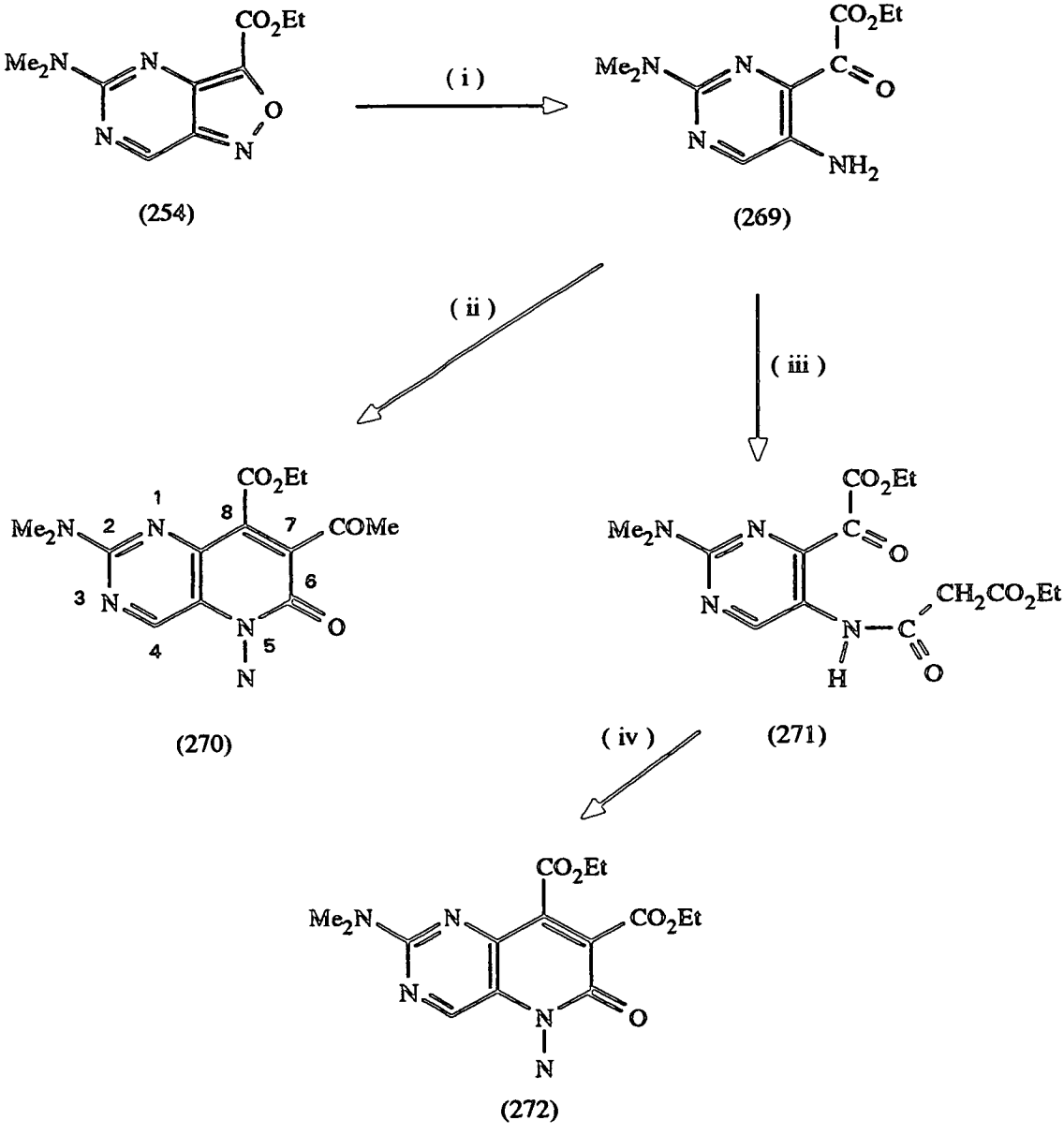
(i) $CH_2(CN)_2$, NaH, DMF, room temp.
(ii) 30% H_2O_2 aqu., 1M NaOH aqu., room temp.

Scheme 80

important contributing factor accounting for these behavioural diferences. However due to time constraints further investigations on the pyrolysis of these pyrimidine derivatives were not undertaken.

In light of the behaviour of structurally similar pyridine derivatives described in Chapter 2, it was considered of interest to briefly examine the oxidation reactions of the nitropyrimidinylmalonate derivatives which had already been synthesised during the present studies. This investigation was undertaken to acertain whether the malonate side chain in these compounds could be oxidised in a fashion similar to that discussed for the nitropyridinylmalonates in Chapter 2, Section 2.4 of this thesis. Therefore diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)malonate (253) was treated (Scheme76) with peracetic acid but this gave only a complex mixture of products. However the oxidation of the diester (253) by alkaline hydrogen peroxide afforded the anticipated diethyl 2-hydroxy-2-(2-dimethylamino-5-nitropyrimidin-4-yl)malonate (255), albeit in only 13% yield. The remainder of the isolated material was unreacted diester (253) (52%). Despite these poor results, the peracetic acid oxidation of the malonate derivative (258) was next attempted (Scheme 77). This fortunately afforded the desired diethyl 2-hydroxy-2-(6-methoxy-5-nitropyrimidin-4-yl)malonate (260) and in good yield (77%). Disappointing however was the oxidation (Scheme 78) of the nitrouracilmalonate derivative (262) which on treatment with peracetic acid gave only an inseparable mixture of products.

The oxidation reaction of 2-cyano-2-(3-nitropyrid-2-yl)ethanenitrile to give 3-nitropyridine-2-carboxylic acid was discussd in Chapter 2, Section 2.4 of this thesis and it was next decided to investigate whether structurally similar pyrimidine derivatives could be oxidised to afford pyrimidinecarboxylic acids. Therefore (Scheme 79), 2-(2-dimethylamino-5-nitropyrimidin-4-yl)malononitrile (265) was prepared in high yield (77%) by the reaction of the chloronitropyrimidine (252) with the anion of malononitrile. The malononitrile derivative (265) was then treated with alkaline hydrogen peroxide and afforded the pyrimidinecarboxylic acid



(i) H_2, Pd-C, EtOAc, room temp.

(ii) $MeCOCH_2CO_2Et$, xylene, mol. sieves 5A, reflux.

(iii) EtO_2CCH_2COCl, benzene, reflux.

(iv) Et_3N, EtOH, reflux.

Scheme 81

derivative (266), isolated as its hemihydrate, in moderate yield (35%). Also isolated from this reaction was some unreacted starting material (265) (15%). Similarly (Scheme 80) diethyl 2-(6-methoxy-5-nitropyrimidin-4-yl)malononitrile (267) was prepared from the chloronitropyrimidine (257) in 73% yield and was then treated with alkaline hydrogen peroxide. In this case no oxidation took place and the starting material was recovered in high yield (83%). Further studies on the oxidation reactions of the pyrimidinylmalononitriles (265) and (267) were not undertaken due to time limitations.

Finally (Scheme 81), the exploitation of one of the new isoxazolopyrimidine derivatives in heterocyclic synthesis was investigated. In this context the isoxazolopyrimidine (254) was hydrogenated over a palladium catalyst to afford a quantitative yield of ethyl 2-(2-dimethylamino-5-aminopyrimidin-4-yl)-2-oxoethanoate (269) as an unstable red oil which required storage at -20^{o} to prevent significant decomposition. In refluxing xylene solution with removal of any volatile by-products (water and ethanol) by molecular sieves the 2-aminopyrimidinyl ketone (269) condensed with ethyl acetoacetate to afford the anticipated pyrido[3,2-d] pyrimidine derivative (270) in moderate yield (56%). The 2-aminopyrimidinyl ketone (269) also condensed with ethyl malonyl chloride to give a quantitative yield of the unstable amide derivative (271). This compound underwent base-catalysed cyclisation in refluxing ethanol in the presence of triethylamine to give the diethyl pyrido[3,2-d]pyrimidine-7,8-dicarboxylate derivative (272) in 60% overall yield.

Studies on the reduction of the remaining two isoxazolopyrimidine derivatives (259) and (263) which were available and subsequent annulation of the *ortho*-amino carbonyl compounds produced were not undertaken during the present studies due to the lack of time available. However it is likely that they would behave similarly to the dimethylaminoisoxazolopyrimidine derivative (254) and afford by reduction the corresponding 2-aminopyrimidyl ketones and thence by

condensation with β-keto ester derivatives and related processes fused pyrimidine derivatives.

3.2 : Experimental

General Experimental Details

For general experimental details see Chapter 2, Section 2.9, pages 80-81.

Elemental Analyses and Mass Spectroscopic Data

Elemental analyses and mass spectroscopic data are collected in Table 15, page 249.

1,1-Dimethylguanidinium Sulphate

1,1-Dimethylguanidinium sulphate was prepared by the reaction of S-methylisothiouronium sulphate with aqueous dimethylamine as described by Weddell[131] as a colourless solid (yield 73%), m.p. 291-294° (decomp.) [lit.,[131] 285-288° (decomp.)].

2-Dimethylaminopyrimidin-4(3H)-one

2-Dimethylaminopyrimidin-4(3H)-one was prepared by the acid-catalysed reaction of 1,1-dimethylguanidinium sulphate with malic acid as described by Overberger and Kogon[132] as a tan solid (yield 95%), m.p. 175-178° (lit.,[132] 175-176°).

2-Dimethylamino-5-nitropyrimidin-4(3H)-one

A mixture of fuming nitric acid (d = 1.5) (33.6ml) and concentrated sulphuric acid (33.6ml) was stirred and cooled to 10° (ice-water bath) then treated portionwise with 2-dimethylaminopyrimidin-4(3H)-one (41.7g; 0.3mol) at such a rate that the reaction temperature did not exceed 70°. After the addition was complete the mixture was stirred and heated at 100° (steam bath) for 4h.

The mixture was poured onto ice (350g) and the precipitated solid was collected to afford 2-dimethylamino-5-nitropyrimidin-4(3H)-one (25.7g; 47%) as a colourless powder, m.p. 303-305° (decomp.) [lit.,[128] 304-311° (decomp.)].

4-Chloro-2-dimethylamino-5-nitropyrimidine (252)

4-Chloro-2-dimethylamino-5-nitropyrimidine (252) was prepared by the reaction of 2-dimethylamino-5-nitropyrimidin-4(3H)-one with phosphorus oxychloride and *N,N*-diethylaniline as described by D.G Saunders[128] as a yellow solid (yield 86%), m.p. 143-147° (lit.,[128] 143°).

4-Hydroxy-5-nitropyrimidin-6(1H)-one

4-Hydroxy-5-nitropyrimidin-6(1H)-one was prepared by the reaction of 4-hydroxypyrimidin-6(1H)-one with fuming nitric acid (d = 1.52) as described by Boon, Jones and Ramage[133] as a cream solid (yield 64%), m.p. >360° (lit.,[133] >300°).

4,6-Dichloro-5-nitropyrimidine

4,6-Dichloro-5-nitropyrimidine was prepared by the reaction of 4-hydroxy-5-nitropyrimidin-6(1H)-one with phosphorus oxychloride and *N,N*-diethylaniline as described by Boon, Jones and Ramage[133] as a brown solid (yield 46%), m.p. 90-95° (lit.,[133] 101-102°).

4-Chloro-6-methoxy-5-nitropyrimidine (257)

4-Chloro-6-methoxy-5-nitropyrimidine (257) was prepared by the reaction of 4,6-dichloro-5-nitropyrimidine with sodium methoxide as described by Taylor, Barton and Paudler[129] as a tan solid (yield 35%), m.p. 64-66° (lit.,[129] 65-66°).

6-Chloro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione

6-Chloro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione was prepared by the reaction of 1,3-dimethylbarbituric acid with phosphorus oxychloride as described by Liao and Cheng[130] as a yellow solid (yield 92%), m.p. 106-110° (lit.,[130] 109-110°).

6-Chloro-1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dione (261)

6-Chloro-1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dione (261) was prepared by the reaction of 6-chloro-1,3-dimethylpyrimidine-2,4(1H,3H)-dione with fuming nitric acid (d = 1.5) and concentrated sulphuric acid as described by Liao and Cheng[130] as a yellow solid (yield 91%), m.p. 76-80° (lit.,[130] 75-80°).

Diethyl 2-(2-Nitropyrimidinyl)propanedioates (253), (258) and (262)

A stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (17.6g; 0.11mol) in anhydrous dimethylformamide (25.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min. The resulting mixture was treated with a solution of the corresponding chloronitropyrimidine derivative (0.05mol) in anhydrous dimethylformamide (25.0ml) and the resulting red mixture was stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) Diethyl 2-(2-Dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253)

The mixture from 4-chloro-2-dimethylamino-5-nitropyrimidine (252) was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary

evaporated and the residue treated with water (75.0ml). The insoluble solid was collected to afford diethyl 2-(2-dimethylamino-5-nitropyrimid-4-yl)propanedioate (253) (91%) which formed cream, irregular crystals, m.p. 89-90° (from hexane-ethyl acetate), ν_{max} 1750-1740 br (C=O) and 1550 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.10 (1H, s, ArH), 5.45 (1H, s, CH), 4.25 (4H, q, J = 7 Hz, 2 x CH_2), 3.28 (3H, s, CH_3), 3.22 (3H, s, CH_3) and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

(ii) Diethyl 2-(6-Methoxy-5-nitropyrimidin-4-yl)propanedioate (258)

The mixture from 4-chloro-6-methoxy-5-nitropyrimidine (257) was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (75.0ml). The mixture was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give an orange oil which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (4:1) gave a yellow oil whose t.l.c. in hexane-diethyl ether (1:1) over silica showed it to contain mainly unreacted diethyl propanedioate.

Elution with hexane-diethyl ether (7:3) afforded diethyl 2-(6-methoxy-5-nitropyrimid-4-yl)propanedioate (258) (69%) as a yellow oil, b.p. 124-126°/ 0.05mmHg, ν_{max} 1755 and 1740 (C=O) and 1538 and 1366 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.78 (1H, s, ArH), 5.00 (1H, s, CH), 4.24 (4H, q, J = 7 Hz, 2 x CH_2), 4.10 (3H ,s, CH_3) and 1.24 (6H, t, J = 7 Hz, 2 x CH_3).

Final elution with methanol gave no further material.

(iii) Diethyl 2-(1,3-Dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262)

The mixture from 6-chloro-1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dione (261) was diluted with water (25.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (75.0ml). The insoluble solid

was collected to afford the sodium salt of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (15.3g) as a red solid, m.p. 280-285° (decomp.). A solution of this sodium salt in water (100ml) was acidified with concentrated hydrochloric acid and the precipitated solid was collected to afford diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (12.0g; 70%) which formed cream, irregular crystals, m.p. 101-104° (from hexane-ethyl acetate), ν_{max} 1750 and 1720-1650 br (C=O) and 1520 and 1330 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 4.97 (1H, s, CH), 4.33 (4H, q, J = 7 Hz, 2 x CH_2), 3.44 (3H ,s, CH_3), 3.43 (3H ,s, CH_3) and 1.33 (6H, t, J = 7 Hz, 2 x CH_3).

Attempted Pyrolysis Reactions of Diethyl 2-(2-Dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253)

(a) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.65g; 0.002mol) in anhydrous toluene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 18h.

The mixture was rotary evaporated to give an orange oil which was triturated with hexane-diethyl ether to afford only unreacted diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.39g; 60%) as a yellow solid, m.p. 85-90°, identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the organic mother liquor gave only a small amount of an orange oil (0.02g) which was not further investigated.

(b) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (1.6g; 0.005mol) in anhydrous xylene (25.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

The mixture was rotary evaporated to give a brown gum which was triturated with hexane-diethyl ether to afford only unreacted diethyl 2-(2-dimethylamino-5-

nitropyrimidin-4-yl)propanedioate (253) (1.2g; 75%) as a brown solid, m.p. 75-77°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the organic mother liquor gave only a small amount of a brown oil (0.10g) which was not further investigated.

(c) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.65g; 0.002mol) in anhydrous diglyme (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated to give a brown oil (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and gums (total = 0.78g) from which no identifiable material could be obtained.

<u>The Pyrolysis Reaction of Diethyl 2-(2-Dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) in Aqueous Pyridine</u>

A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (1.6g; 0.005mol) in pyridine (9.0ml) and water (1.0ml) was stirred and heated under reflux for 24h.

The mixture was rotary evaporated and the residue was dissolved in methylene chloride (25.0ml). The solution was washed with 2M aqueous hydrochloric acid (5.0ml) and rotary evaporated to give a red oil (1.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (19:1) afforded 2-dimethylamino-4-methyl-5-nitropyrimidine (256b) (0.075g; 8%) which formed cream needles, m.p. 138-139° (from ethanol), ν_{max} 1538 and 1320 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.02 (1H, s, ArH), 3.28 (6H, s, 2 x CH_3) and 2.72 (3H ,s, CH_3).

Elution with hexane-ethyl acetate (9:1) afforded ethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)ethanoate (256a) (0.37g; 29%) which formed yellow needles, m.p. 80-81° (from ethanol), ν_{max} 1735 (C=O) and 1554 and 1304 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.10 (1H, s, ArH), 4.19 (2H, q, J = 7 Hz, CH_2), 4.10 (2H ,s, CH_2), 3.29 (6H, s, 2 x CH_3) and 1.26 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (9:1) gave unreacted diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.46g; 29%) as a yellow solid, m.p. 82-84°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Final elution with methanol gave an orange gum (0.09g) which was not further investigated.

Ethyl 5-Dimethylaminoisoxazolo[4,3-d]pyrimidine-3-carboxylate (254)

(a) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (1.6g; 0.005mol) in Analar pyridine (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

The mixture was rotary evaporated to give a brown solid (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded ethyl 5-dimethylaminoisoxazolo[4,3-d]pyrimidine-3-carboxylate (254) (0.32g; 27%) which formed orange needles, m.p. 161-163° (from toluene), ν_{max} 1715 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.30 (1H, s, ArH), 4.49 (2H, q, J = 7 Hz, CH_2), 3.35 (6H, s, 2 x CH_3) and 1.45 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (7:3) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils, gums and solids (total = 0.81g) from which no identifiable material could be obtained.

(b) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (1.6g; 0.005mol) in anhydrous xylene (50.0ml) was stirred and heated under reflux for 24h using a 20cm vigreux column in such a way that any ethanol produced would distil over without distillation of the xylene.

Rotary evaporation of the mixture gave an orange solid (0.90g), m.p. 140-150°, which was crystallised from toluene to afford ethyl 5-dimethylaminoisoxazolo [4,3-d]pyrimidine-3-carboxylate (254) (0.48g; 41%) as orange needles, m.p. 162-164°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the toluene mother liquor gave only a multicomponent brown gum (0.22g) from which no identifiable material could be obtained.

(c) A solution of diethyl 2-(2-dimethylamino-5-nitropyrimid-4-yl)propanedioate (253) (1.6g; 0.005mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 18h.

The mixture was rotary evaporated to give a gummy solid which was washed with hexane-toluene to afford ethyl 5-dimethylaminoisoxazolo[4,3-d]pyrimidine-3-carboxylate (254) (0.94; 79%) as an orange solid, m.p. 151-154°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Rotary evaporation of the organic mother liquor gave a brown gum (0.10g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was therefore not further investigated.

Ethyl 7-Methoxyisoxazolo[4,3-d]pyrimidine-3-carboxylate (259)

A solution of diethyl 2-(6-methoxy-5-nitropyrimid-4-yl)propanedioate (258) (2.5g; 0.008mol) in anhydrous xylene (100ml) was stirred and heated under reflux with

exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 24h.

The mixture was rotary evaporated to give a brown solid (2.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a multicomponent, orange oil (0.47g) which was not further investigated.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 7-methoxyisoxazolo[4,3-d]pyrimidine-3-carboxylate (259) (1.2g; 67%) which formed colourless needles, m.p. 107-108° (from ethanol), ν_{max} 1733 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.66 (1H, s, ArH), 4.59 (2H, q, J = 7 Hz, CH_2), 4.27 (3H ,s, CH_3) and 1.49 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave no further material.

Pyrolysis Reactions of Diethyl 2-(1,3-Dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262)

(a) A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (3.4g; 0.01mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 1h.

The mixture was rotary evaporated to give a brown oil (3.7g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 4,6-dimethylisoxazolo[4,3-d]pyrimidine-5,7(4H,6H)-dione-3-carboxylate (263) (0.21g; 8%) which formed colourless plates, m.p. 129-130° (from hexane-toluene), ν_{max} 1720, 1675 and 1630 (C=O) (NO_2) cm^{-1}, δ_H ($CDCl_3$) 4.46 (2H, q, J = 7 Hz, CH_2), 3.79 (3H, s, CH_3), 3.45 (3H, s, CH_3) and 1.44 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (7:3) afforded ethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)ethanoate (264) which formed yellow needles, m.p. 123-124° (from hexane-ethyl acetate), ν_{max} 1732, 1713 and 1666 (C=O) and 1516 and 1331 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 4.26 (2H, q, J = 7 Hz, CH_2), 3.77 (2H, s, CH_2), 3.49 (3H, s, CH_3), 3.40 (3H, s, CH_3) and 1.30 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (7:3) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and gums (total = 1.6g) from which no identifiable could be obtained.

(b) A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (1.7g; 0.005mol) in anhydrous toluene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 5h.

The mixture was rotary evaporated to give a brown oil (1.9g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) afforded ethyl 4,6-dimethylisoxazolo[4,3-d]pyrimidine-5,7(4H,6H)-dione-3-carboxylate (263) (016g; 13%) as a colourless solid, m.p. 120-126°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)ethanoate (264) (0.53g; 39%) as a pink solid, m.p. 95-101°, identified by comparison [m.p., i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

Final elution with methanol gave a multicomponent brown gum (0.35g) which was not further investigated.

(c) A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (1.7g; 0.005mol) in Analar pyridine (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to give a brown gum (1.7g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) afforded ethyl 4,6-dimethylisoxazolo [4,3-d]pyrimidine-5,7(4H,6H)-dione-3-carboxylate (263) as a colourless solid (0.22g; 17%), m.p. 120-122°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) through to ethyl acetate and then finally with methanol gave only a series of complex solids (total = 0.38g) from which no identifiable could be obtained.

(d) A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (0.69g; 0.002mol) in anhydrous toluene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to give an orange oil which was triturated with diethyl ether to give only unreacted diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (0.43g; 62%) as an orange solid, m.p. 96-99°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Rotary evaporation of the ethereal mother liquour gave a multicomponent orange gum (0.07g) which was not further investigated.

(e) Repetition of the above reaction with heating under reflux for 24h gave, after rotary evaporation of the reaction mixture, an intractable multicomponent brown gum (0.55g) which was not further investigated.

Ethyl 2-(1,3-Dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)ethanoate (264)

A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (1.7g; 0.005mol) in pyridine (9.0ml) and water (1.0ml) was stirred and heated under reflux for 15 min.

The mixture was rotary evaporated and the residue was dissolved in methylene chloride (25.0ml). The resulting solution was washed with 2M aqueous hydrochloric acid (5.0ml) and rotary evaporated to afford ethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)ethanoate (264) (1.3g; 96%) as a yellow solid, m.p. 118-122°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

The Attempted Oxidation of Diethyl 2-(2-Dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253)

A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.98g; 0.003mol) in glacial acetic acid (15.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (7.5ml) and the resulting mixture was stirred and heated at 50^0 (oil bath) for 21h.

The mixture was concentrated by rotary evaporation to one half of the original volume, diluted with water (10.0ml) and the resulting solution extracted with methylene chloride (3 x 20.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (10.0ml) and rotary evaporated to give a yellow oil (0.20g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a four component mixture which was not further investigated.

Diethyl 2-(2-Dimethylamino-5-nitropyrimidin-4-yl)-2-hydroxypropanedioate (255)

A solution of diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)propanedioate (253) (0.98g; 0.003mol) in 1M aqueous sodium hydroxide (10.0ml) was treated with 30% w/w aqueous hydrogen peroxide solution (2.0ml) and the resulting solution was stirred at room temperature for 2h.

The mixture was neutralised by the addition of 2M aqueous hydrochloric acid then solid sodium acetate and extracted with methylene chloride (3 x 50.0ml) to give a yellow solid (0.79g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave only unreacted diethyl 2-(2-dimethylamino-5-nitropyrimid-4-yl)propanedioate (253) (0.51g; 52%) as a yellow solid. m.p. 87-89°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with hexane-ethyl acetate (4:1) afforded diethyl 2-(2-dimethylamino-5-nitropyrimidin-4-yl)-2-hydroxypropanedioate (255) (0.14g; 13%) which formed yellow, irregular crystals, m.p. 107-108° (from hexane-ethyl acetate), ν_{max} 3405 (OH), 1762 and 1733 (C=O) and 1554 and 1308 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.08 (1H, s, ArH), 4.32 (4H, q, J = 7 Hz, 2 x CH_2), 4.2-3.9 (1H, bs, OH) (exch.), 3.30 (3H, s, CH_3), 3.23 (3H, s, CH_3) and 1.29 (6H, t, J = 7 Hz, 2 x CH_3).

Final elution with methanol gave no material.

Diethyl 2-Hydroxy-2-(6-methoxy-5-nitropyrimidin-4-yl)propanedioate (260)

A solution of diethyl 2-(6-methoxy-5-nitropyrimidin-4-yl)propanedioate (258) (1.3g; 0.004mol) in glacial acetic acid (20.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (10.0ml) and the resulting mixture was stirred and heated at 50^0 (oil bath) for 16h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (10.0ml) and the resulting solution extracted with methylene chloride (3 x 25.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (10.0ml) and rotary evaporated to afford diethyl 2-hydroxy-2-(6-methoxy-5-nitropyrimidin-4-yl)propanedioate (260) (1.0g; 77%) which formed yellow plates, m.p. 87-88° (from hexane-ethyl acetate), ν_{max} 3279 (OH), 1758 and 1734 (C=O) and 1530 and 1373 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.74 (1H, s, ArH), 4.36 (2H, q, J = 7 Hz, CH_2), 4.35 (2H, q, J = 7 Hz, CH_2), 4.11 (3H, s, CH_3) and 1.30 (6H, t, J = 7 Hz, 2 x CH_3).

The Attempted Oxidation of Diethyl 2-(1,3-Dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262)

A solution of diethyl 2-(1,3-dimethyl-5-nitropyrimidine-2,4(1H,3H)-dion-6-yl)propanedioate (262) (1.0g; 0.003mol) in glacial acetic acid (15.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (7.5ml) and the resulting mixture was stirred and heated at 50^0 (oil bath) for 17h.

The mixture was concentrated by rotary evaporation to one half of its original volume then diluted with water (10.0ml) and the resulting solution extracted with methylene chloride (3 x 25.0ml). The extracts were washed with saturated aqueous sodium thiosulphate solution (5.0ml) and rotary evaporated to give a waxy, yellow solid (0.32g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be an unresolvable, six component mixture which was not further investigated.

2-Cyano-2-(5-nitropyrimidin-4-yl)ethanenitriles (265) and (267)

A stirred suspension of sodium hydride (1.1g; 0.044mol) in anhydrous dimethylformamide (20.0ml) was cooled to 0^o (ice-salt bath) and was treated dropwise with a solution of malononitrile (2.9g; 0.044mol) in anhydrous dimethylformamide (10.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15 min. The mixture was then treated dropwise with a solution of the corresponding chloronitropyrimidine (0.02mol) in anhydrous dimethylformamide (10.0ml) and the resulting solution was stirred at room temperature with exclusion of atmospheric moisture for 2h and then worked up as described for the individual reactions below.

(i) 2-Cyano-2-(2-dimethylamino-5-nitropyrimidin-4-yl)ethanenitrile (265)

The mixture from 4-chloro-2-dimethylamino-5-nitropyrimidine (252) was diluted with water (10.0ml) and stirred at room temperature for 10 min then rotary

evaporated and the residue treated with water (25.0ml). The resulting mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to afford 2-cyano-2-(2-dimethylamino-5-nitropyrimidin-4-yl)ethanenitrile (265) as a hemihydrate (77%) which formed brown needles, m.p. 155-158° (from dimethylformamide-water), ν_{max} 3620 and 3426 br (NH and OH), 2206 and 2185 (CN), 1643 (C=C) and 1529 and 1350 (NO_2) cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.53 (1H, s, ArH) and 3.14 (6H, s, 2 x CH_3).

Extraction of the aqueous mother liquor with methylene chloride gave a multicomponent brown oil which was therefore not further investigated.

(ii) 2-Cyano-2-(6-methoxy-5-nitropyrimidin-4-yl)ethanenitrile (267)

The mixture from 4-chloro-6-methoxy-5-nitropyrimidine (257) was diluted with water (10.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (25.0ml). The resulting mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to afford 2-cyano-2-(6-methoxy-5-nitropyrimidin-4-yl)ethanenitrile (267) (3.2g; 73%) which formed yellow, irregular crystals, m.p. 159° (decomp.) (from dimethylformamide-water), ν_{max} 3063 (NH), 2211 and 2190 (CN), 1620 (C=C) and 1534 and 1333 (NO_2) cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.22 (1H, s, ArH), 7.8-7.0 (1H, bs, NH) (exch.) and 3.90 (3H, s, CH_3).

Extraction of the aqueous mother liquor with methylene chloride gave a complex red oil (1.9g) which was not further investigated.

2-Dimethylamino-5-nitropyrimidine-4-carboxylic Acid (266)

A solution of 2-cyano-2-(2-dimethylamino-5-nitropyrimidin-4-yl)ethanenitrile (265) (0.93g; 0.004mol) in 1M aqueous sodium hydroxide (10.0ml) was treated with 30% w/v aqueous hydrogen peroxide solution (2.0ml) and the mixture was stirred at

room temperature for 2h. The reaction temperature rose to 40^0 after 1.5h and was kept at this temperature by the application of an ice-water cooling bath when necessary.

The mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to give unreacted 2-cyano-2-(2-dimethylamino-5-nitropyrimidin-4-yl)ethanenitrile (265) (0.14g; 15%) as a yellow solid, m.p. 150-155°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Extraction of the aqueous mother liqour with methylene chloride afforded 2-dimethylamino-5-nitropyrimidine-4-carboxylic acid (266) as a hemi-hydrate (0.30g; 35%) which formed yellow, irregular crystals, m.p. 200-202° (from water), ν_{max} 3000-2000 br (OH), 1727 (C=O) and 1554 and 1328 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2S=O]$ 9.09 (1H, s, ArH), 5.50 (1H, bs, OH) (exch.) and 3.30 (6H, s, 2 x CH_3).

The Attempted Oxidation of 2-Cyano-2-(6-methoxy-5-nitropyrimidin-4-yl)ethanenitrile (267)

A solution of 2-cyano-2-(6-methoxy-5-nitropyrimidin-4-yl)ethanenitrile (267) (1.1g; 0.005mol) in 1M aqueous sodium hydroxide (12.5ml) was treated with 30% w/v aqueous hydrogen peroxide solution (2.5ml) and the mixture was stirred at room temperature for 2h.

The mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was collected to give unreacted 2-cyano-2-(6-methoxy-5-nitropyrimidin-4-yl)ethanenitrile (267) (0.91g; 83%) as a yellow solid, m.p. 158° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride (3 x 25.0ml) gave no further material.

Ethyl 2-(5-Amino-2-dimethylaminopyrimidin-4-yl)-2-oxoethanoate (269)

A solution of ethyl 5-dimethylaminoisoxazolo[4,3-d]pyrimidine-3-carboxylate (254) (1.55g; 0.0065mol) in ethyl acetate (200ml) was hydrogenated

over 10% palladium-on-charcoal (0.16g) at room temperature and atmospheric pressure for 2h.

The mixture was filtered through celite and the filtrate was rotary evaporated to afford ethyl 2-(5-amino-2-dimethylaminopyrimidin-4-yl)-2-oxoethanoate (269) (1.6g; 100%) as a red oil, b.p. 104°/ 0.05mmHg, ν_{max} 3464 and 3351 (NH) and 1739 and 1672 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.22 (1H, s, ArH), 5.8-4.2 (2H, bs, NH_2) (exch.), 4.39 (2H, q, J = 7 Hz, CH_2), 3.04 (6H, s, 2 x CH_3) and 1.37 (3H, t, J = 7 Hz, CH_3).

Ethyl 7-Acetyl-2-dimethylaminopyrido[3,2-d]pyrimidin-6(5H)-one-8-carboxylate (270)

A solution of ethyl 2-(5-amino-2-dimethylaminopyrimidin-4-yl)-2-oxoethanoate (269) (0.48g; 0.002mol) and ethyl 3-oxobutanoate (0.26g; 0.002mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 5h and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 5h.

The mixture was cooled to 10^0 (ice-water bath) and the insoluble solid was collected to afford ethyl 7-acetyl-2-dimethylaminopyrido[3,2-d]pyrimid-6(5H)-one-8-carboxylate (270) (0.34g; 56%) which formed orange needles, m.p. 268-269° (from glacial acetic acid), ν_{max} 3100-2500 br (NH,OH) and 1733, 1695 and 1667 (C=O) cm^{-1}, δ_H[$(CD_3)_2S$=O] 12.5-11.5 (1H, bs, NH or OH) (exch.), 8.62 (1H, s, ArH), 4.33 (2H, q, J = 7 Hz, CH_2), 3.10 (6H, s, 2 x CH_3), 2.53 (3H, s, CH_3) and 1.30 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the xylene mother liquor gave only a multicomponent brown gum (0.13g) which was not further investigated.

Ethyl 2-[2-Dimethylamino-5-(2-ethoxycarbonylethanoylamino)pyrimidin-4-yl]-2-oxoethanoate (271)

A solution of ethyl 2-(5-amino-2-dimethylaminopyrimidin-4-yl)-2-oxoethanoate (269) (0.95g; 0.004mol) in anhydrous benzene (10.0ml) was treated dropwise with a solution of ethyl malonyl chloride (0.60g; 0.004mol) in anhydrous benzene (10.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated to afford ethyl 2-[2-dimethylamino-5-(2-ethoxycarbonylethanoylamino)pyrimidin-4-yl]-2-oxoethanoate (271) (1.3g; 100%) as a brown oil, ν_{max} 3336 (NH) and 1743 and 1694 (C=O) cm^{-1}, δ_H ($CDCl_3$) 10.5 (1H, bs, NH) (exch.), 9.65 (1H, s, ArH), 4.40 (2H, q, J = 7 Hz, CH_2), 4.27 (2H, q, J = 7 Hz, CH_2), 3.49 (2H, s, CH_2), 3.12 (6H, s, 2 x CH_3), 1.37 (3H, t, J = 7 Hz, CH_3) and 1.29 (3H, t, J = 7 Hz, CH_3), which could not be further purified by high vacuum distillation due to its thermal instability.

Diethyl 2-Dimethylaminopyrido[3,2-d]pyrimidin-6(5H)-one-7,8-dicarboxylate (272)

A solution of ethyl 2-[2-dimethylamino-5-(2-ethoxycarbonylethanoylamino) pyrimidin-4-yl]-2-oxoethanoate (271) (0.70g; 0.002mol) in anhydrous ethanol (10.0ml) was treated with triethylamine (0.81g; 0.008mol) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

Rotary evaporation of the mixture followed by trituration of the residue with ethanol afforded diethyl 2-dimethylaminopyrido[3,2-d]pyrimidin-6(5H)-one-7,8-dicarboxylate (272) (0.40g; 60%) which formed orange needles, m.p. 186-187° (from ethanol), ν_{max} 3100-2500 br (NH,OH) and 1744 and 1651 (C=O) cm^{-1}, δ_H[$(CD_3)_2S$=O] 8.71 (1H, s, ArH), 4.46 (2H, q, J = 7 Hz, CH_2), 4.41 (2H, q, J = 7 Hz, CH_2), 3.16 (6H, s, 2 x CH_3), 1.41 (3H, t, J = 7 Hz, CH_3) and 1.38 (3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the ethanolic mother liquor gave a multicomponent red gum (0.21g) which was not further investigated.

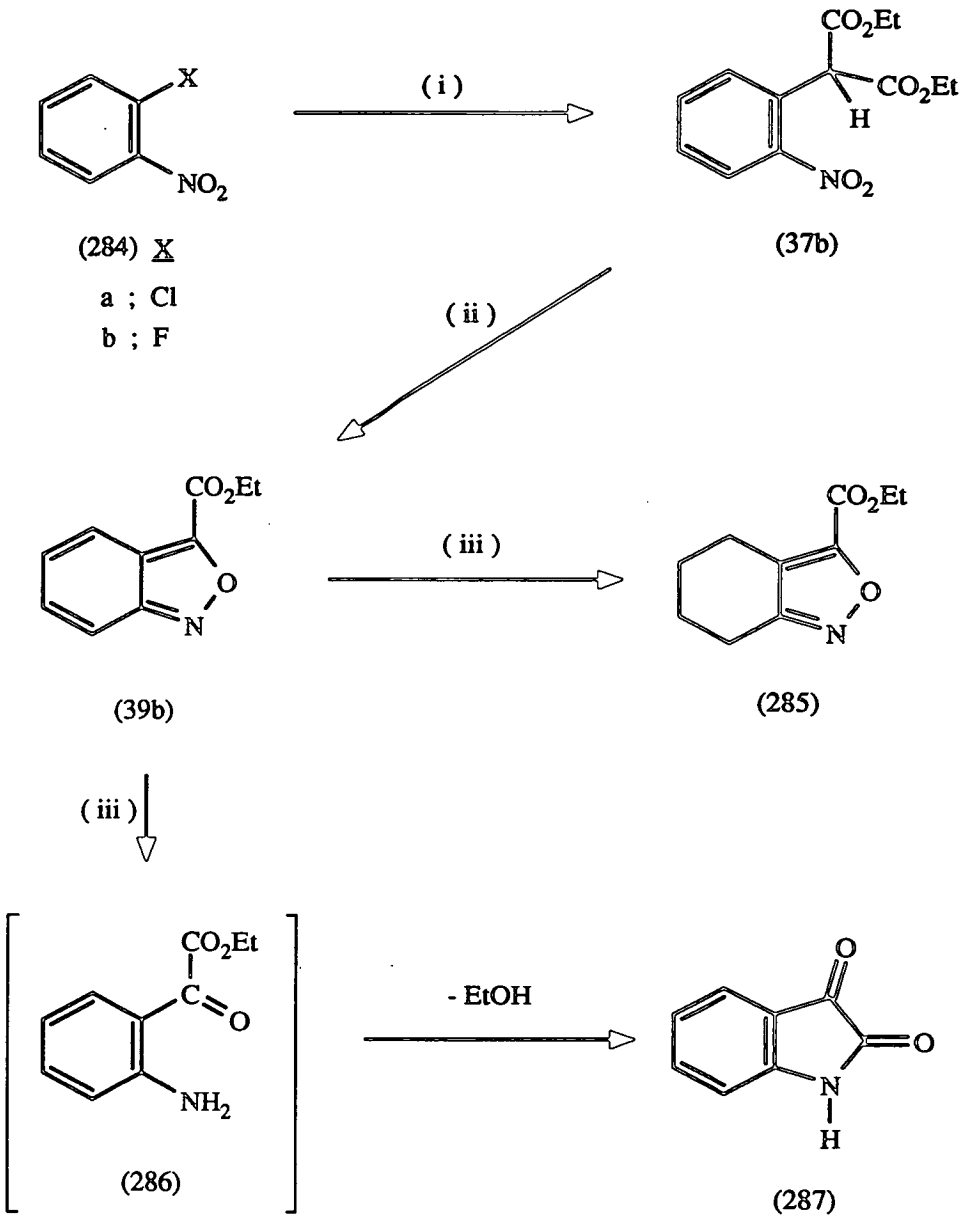
Table 15 : Elemental Analyses and Mass Spectroscopic Data

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)^a$
(253) ($C_{13}H_{18}N_4O_6$)	47.8	5.4	17.1	326	47.9	5.5	17.2	326
(254) ($C_{10}H_{12}N_4O_3$)	50.6	5.1	23.3	236	50.8	5.1	23.7	236
(255) ($C_{13}H_{18}N_4O_7$)	45.6	5.3	16.3	342	45.6	5.3	16.4	342
(256a) ($C_{10}H_{14}N_4O_4$)	47.1	5.4	22.0	254	47.2	5.5	22.0	254
(256b) ($C_7H_{10}N_4O_2$)	46.1	5.4	29.7	182	46.2	5.5	30.8	182
(258) ($C_{12}H_{15}N_3O_7$)	45.9	4.8	13.3	(314)	46.0	4.8	13.4	313
(259) ($C_9H_9N_3O_4$)	48.2	4.1	18.6	(224)	48.4	4.0	18.8	223
(260) ($C_{12}H_{15}N_3O_8$)	43.6	4.6	12.9	(330)	43.8	4.6	12.8	329
(262) ($C_{13}H_{17}N_3O_8$)	45.5	4.9	12.1	(344)	45.5	5.0	12.2	343
(263) ($C_{10}H_{11}N_3O_5$)	47.3	4.1	16.4	253	47.4	4.3	16.6	253
(264) ($C_{10}H_{13}N_3O_6$)	44.3	4.8	15.4	271	44.3	4.8	15.5	271
(265) ($C_9H_8N_6O_2.1/2H_2O$)	44.3	4.0	34.3	232.0713	44.8	3.7	34.8	232.0709
(266) ($C_7H_8N_4O_4.1/2H_2O$)	37.5	4.3	25.5	212	38.0	4.1	25.3	212
(267) ($C_8H_5N_5O_3$)	44.1	2.5	31.8	219	43.8	2.3	32.0	219
(269) ($C_{10}H_{14}N_4O_3$)	49.6	6.0	23.0	(239.1144)	50.4	5.9	23.5	(239.1144)
(270) ($C_{14}H_{16}N_4O_4$)	55.0	5.3	18.4	304	55.3	5.3	18.4	304
(271) ($C_{15}H_{20}N_4O_6$)	-	-	-	352.1399	-	-	-	352.1383
(272) ($C_{15}H_{18}N_4O_5$)	54.1	5.5	16.9	334	53.9	5.4	16.8	334

a, molecular ions detected by Electron Impact Mass Spectroscopy or, for values in parentheses, molecular ions detected by Fast Atom Bombardment Mass Spectroscopy.

Chapter 4

Studies on the Synthesis and Reactivity of 2,1-Benzisoxazole Derivatives



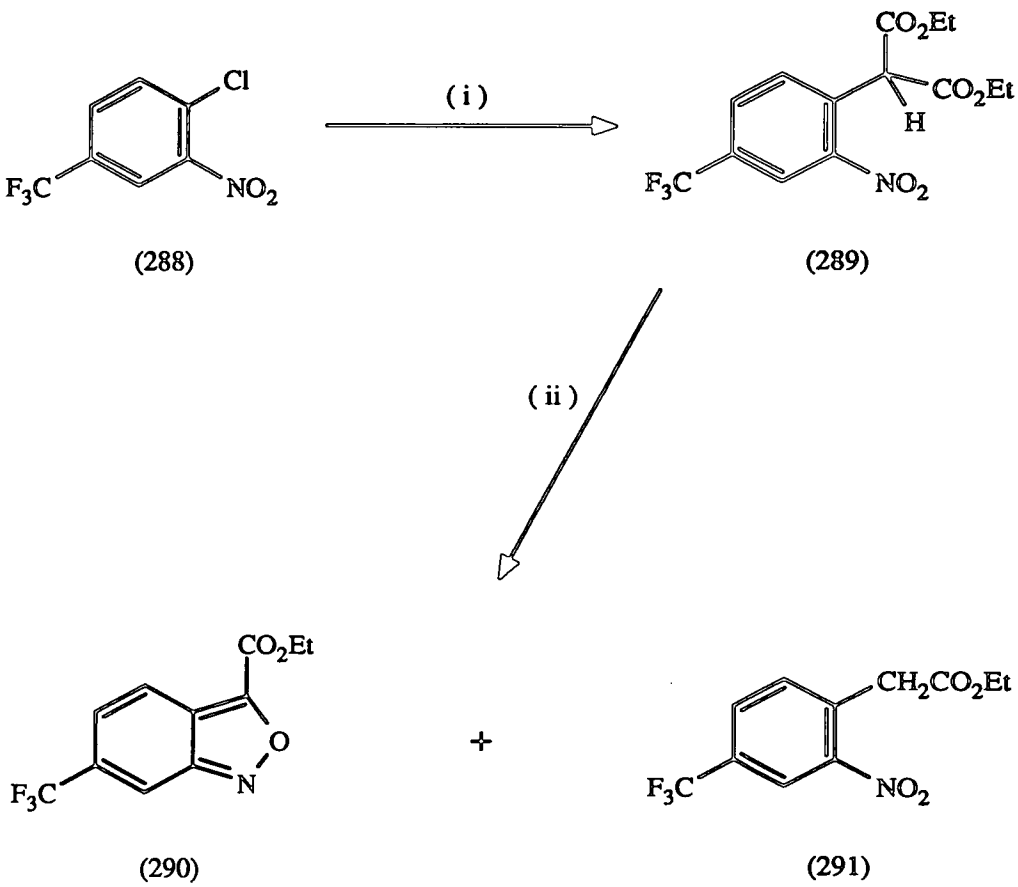
(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100^0.
(ii) xylene, mol. sieves 5A, reflux.
(iii) H_2, Pd-C, EtOAc, room temp.

Scheme 82

4.1 : Studies on the Synthesis and Reactivity of 2,1-Benzisoxazole Derivatives

Chapter 2, Section 2.1 of this thesis describes the many uses of 2,1-benzisoxazoles as precursors for the synthesis of fused heterocycles. It is therefore of interest to increase the accessibility of these important synthetic intermediates by investigating new routes for their synthesis. This chapter is therefore concerned with an investigation on the application of the new fused 3,4-isoxazole synthesis, which was developed during the studies described in Chapters 2 and 3 of this thesis, to the synthesis of 2,1-benzisoxazole derivatives. It is also concerned with the further conversion of the 2,1-benzisoxazoles so produced into other fused heterocycles. With these objectives in mind (Scheme 82) the reaction of 2-chloronitrobenzene (284a) with the anion of diethyl malonate was investigated in an attempt to prepare diethyl 2-(2-nitrophenyl)malonate (37b) whose pyrolysis was then to be studied. Unfortunately these conditions afforded only a low yield (19%) of the desired nitrophenylmalonate (37b) together with unreacted 2-chloronitrobenzene (284a) (50%). However, the more reactive 2-fluoronitrobenzene (284b) condensed readily with the anion of diethyl malonate to afford a quantitative yield of the nitrophenylmalonate (37b). In 1961, Grob and Weissbach reported[16] that the during the purification of the nitrophenylmalonate (37b) by distillation, some ethyl 2,1-benzisoxazole-3-carboxylate (39b) was isolated. An attempt was made to repeat this observation during the present studies, which in this case involved the kugelrohr distillation of the nitrophenylmalonate (37b). However, it was found that the nitro compound (37b) was recovered unchanged after sublimation under reduced pressure at 164°/1.5mmHg. It was next decided to attempt the pyrolysis of the nitrophenylmalonate (37b) in inert solvents. it was found that the nitro compound (37b) was recovered unchanged after heating under reflux in xylene or on heating in dibenzyl ether at 190°. On stronger heating in dibenzyl ether at 250° the nitrophenylmalonate (37b) was converted in low yield (14%) into isatin (287) as the only identifiable product. It may be surmised from this result that the 2,1-

benzisoxazole (39b) is being formed under these conditions but is unstable at the high temperature involved. It can be postulated that thermal ring opening[30,31] of the isoxazole ring in the 2,1-benzisoxazole (39b) would afford a reactive 2-acylnitrene intermediate. This intermediate might then abstract either one or two protons from some species in the reaction mixture and the resulting intermediate might then undergo intramolecular cyclisation to finally give isatin (287). However, further investigations into the mode of formation of isatin (287) by the thermal decomposition of the nitrophenylmalonate (37b) were not undertaken. As discussed in Chapters 2 and 3 of this thesis, the efficient pyrolysis of diethyl nitroheteroarylmalonate derivatives to afford fused 3,4-isoxazoles is dependant on the removal of ethanol from the reaction mixture. Therefore, the nitrophenylmalonate (37b) was heated under reflux in xylene in the presence of molecular sieves to remove any ethanol by-product. It was gratifying that these conditions afforded a good yield (63%) of the anticipated 2,1-benzisoxazole derivative (39b) after 100h. Also isolated was some unreacted starting material (37b) (16%). An attempt was next made to improve the yield of the 2,1-benzisoxazole (39b) by heating the nitrophenylmalonate (37b) under reflux in the higher boiling mesitylene, again in the presence of molecular sieves. However, only a complex mixture of products was formed under these conditions. It is of interest to compare the rate of decomposition in refluxing xylene of the nitrophenylmalonate (37b) with that of the analogous nitropyridylmalonate derivative (102a) (see Chapter 2, Section 2.2). The benzene derivative was converted much more slowly into a fused 3,4-isoxazole than the corresponding pyridine derivative. The reason for this difference may be due to the increased electron-deficiency of a pyridine ring as compared with a benzene ring making the C-H bond in the malonate side-chain of the nitropyridylmalonate (102a) weaker than that of its benzene counterpart (37b). This decrease in bond strength should therefore make thermal elimination of ethanol from the malonate, to give a ketene, more facile. With this in mind, it was anticipated that putting an additional electron-withdrawing group in the ring of a nitrophenylmalonate derivative should



(288) (289) (290) (291)

(i) $CH_2(CO_2Et)_2$, NaH, DMF, 100^0.
(ii) xylene, mol. sieves 5A, reflux.

Scheme 83

increase the rate of its pyrolysis. It was therefore decided (Scheme 83) to synthesise the trifluoromethyl compound (289) and to study its pyrolysis. The trifluoromethyl derivative (289) was readily prepared in high yield (90%) by the reaction of the chloronitrobenzene derivative (288) with the anion of diethyl malonate. The trifluoromethyl derivative (289) was heated under reflux in xylene in the presence of molecular sieves and did indeed pyrolyse more rapidly than the analogous compound lacking the trifluoromethyl group. Only a small amount (8%) of unreacted starting material (289) was recovered after 48h under these conditions. However, the yield of the desired 2,1-benzisoxazole (290) was disappointingly low (26%). As well as this anticipated pyrolysis product, a comparable amount (26%) of the nitrophenylacetate derivative (291) was isolated. Due to the low yield of the 2,1-benzisoxazole (290) and the production of the unwanted by-product (291) further investigations on the pyrolysis of the trifluoromethyl compound were not undertaken.

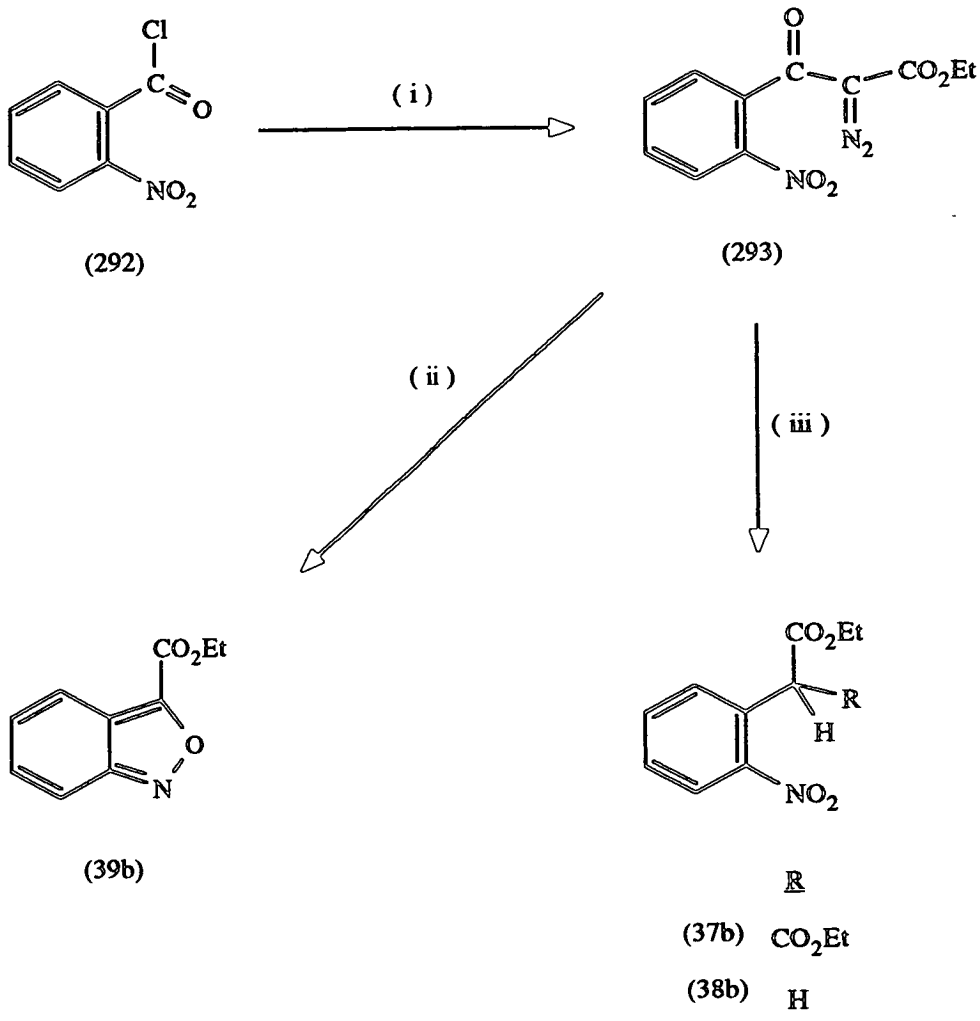
Heating diethyl nitroheteroarylmalonate derivatives under reflux in aqueous pyridine was shown in Chapters 2 and 3 to result in the loss of one ethoxycarbonyl group from the malonate affording ethyl nitroheteroarylacetate derivatives. In an attempt to extend the scope of this reaction to analogous benzene derivatives, diethyl 2-(2-nitrophenyl)malonate (37b) was heated under reflux in aqueous pyridine. It was pleasing to find that a high yield (76%) of the anticipated ethyl 2-(2-nitrophenyl) acetate (38b) was isolated under these condtions. In a further investigation of scope of this reaction, the pyrolysis of diethyl 2-phenylmalonate in aqueous pyridine was attempted. However, these conditions resulted in the isolation of only unreacted starting material in high yield, no cleavage reaction being observed.

At this point it was deemed of interest to study the pyrolysis in refluxing xylene of diethyl 2-(4-nitrophenyl)malonate and compare its rate of decomposition with that of the analogous pyridine derivative, diethyl 2-(5-nitropyrid-2-yl)malonate (121), under the same conditions. A similar comparison between the pyrolysis rates of diethyl 2-(2-nitrophenyl)malonate (37b) and diethyl 2-(3-nitropyrid-2-yl)malonate (102a) was

discussed earlier in this chapter. The strength of the C-H bond in the malonate side-chain in the pyridine derivative (121) should be weaker than that of the corresponding benzene derivative and therefore diethyl 2-(4-nitrophenyl)malonate should undergo thermal decomposition to a ketene more slowly than its pyridine analogue. Diethyl 2-(4-nitrophenyl)malonate was prepared by the reaction of 4-fluoronitrobenzene with the anion of diethyl malonate and its pyrolysis in xylene in the presence of molecular sieves was examined. After 48h under these conditions only a high yield of unreacted starting material was isolated. Again the nitrophenylmalonate derivative does pyrolyse more slowly than its corresponding nitropyridylmalonate analogue (121) since the latter was previously shown (see Chapter 2, Section 2.3, page 35) to decompose completely after 48h under identical molecular sieve-mediated conditions.

With the successful synthesis of ethyl 2,1-benzisoxazole-3-carboxylate (39b) having been established, it was next decided to investigate its reduction (Scheme 82) in the expectation of obtaining the 2-aminophenylketone derivative (286) with a view to studying the annulation reactions of the latter. Therefore the 2,1-benzisoxazole (39b) was hydrogenated over a palladium catalyst and afforded a mixture of products. The major product isolated from this mixture was identified as the known[134] tetrahydro-2,1-benzisoxazole (285) (40%). A similar instance in which the benzene ring of a 2,1-benzisoxazole derivative was reduced in preference to the reductive ring opening of the isoxazole ring has been reported.[135] The only other product which was obtained by the catalytic reduction of the 2,1-benzisoxazole (39b) was identified as isatin (287). This product is presumably being formed by intramolecular cyclisation of the initially produced 2-aminophenylketone derivative (286). As initial studies of the reductive opening of the isoxazole ring in the 2,1-benzisoxazole (39b) had proved disappointing it was decided not to investigate this process any further.

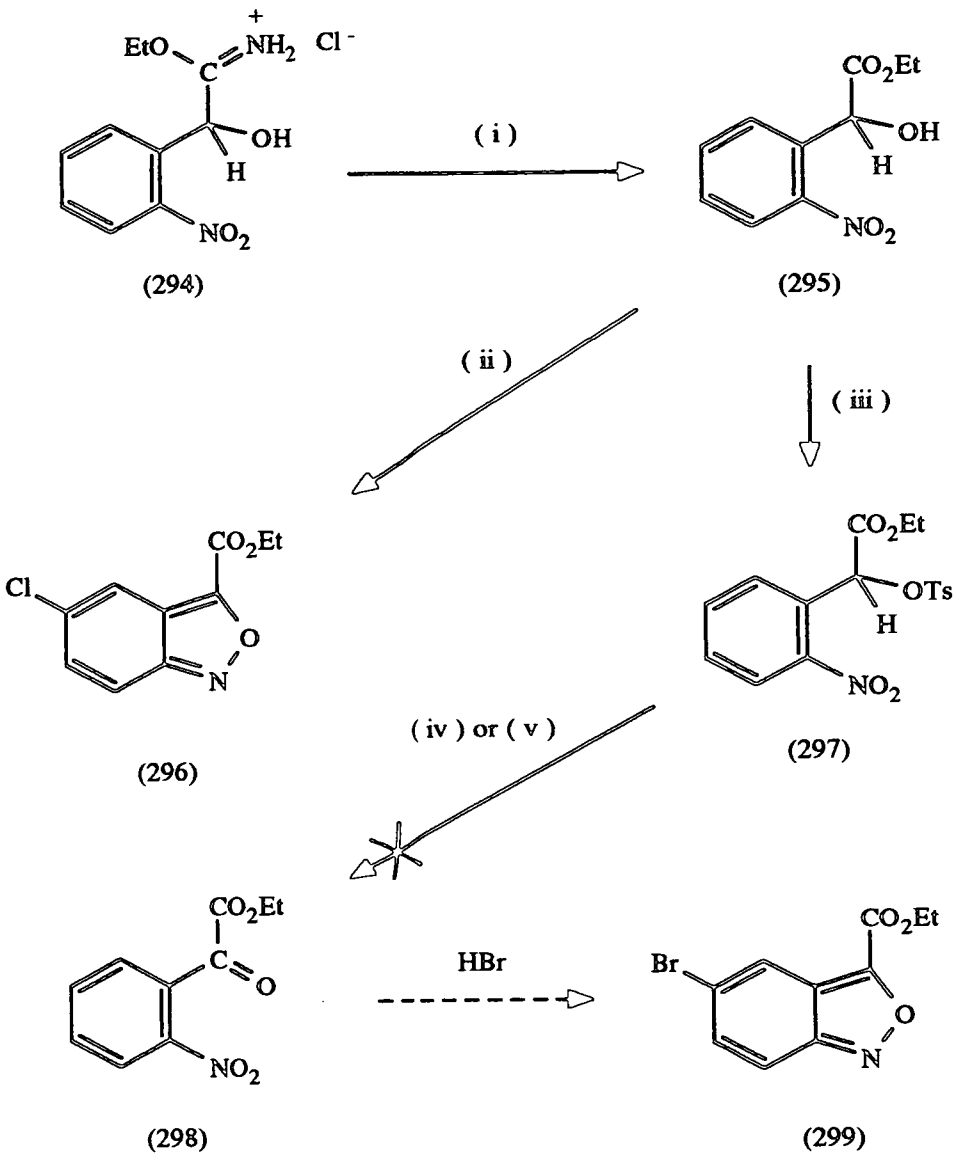
The many diverse methods for the synthesis of 2,1-benzisoxazoles were reviewed in Chapter 1 of this thesis. Due to the long reaction time required and the moderate yield obtained for the synthesis of the 2,1-benzisoxazole derivative (39b) via



(i) $EtO_2CCH{=}N_2$, 50^0.
(ii) toluene, reflux.
(iii) hν, EtOH, room temp.
(iv) hν, MeCN, room temp.

Scheme 84

the pyrolysis of diethyl 2-(2-nitrophenyl)malonate (37b) it was deemed of interest to investigate alternative methods for the synthesis of such 3-substituted 2,1-benzisoxazoles in the hope of finding a more expeditious route. The pyrolysis of ethyl 2-diazo-3-(2-nitroheteroaryl)-3-oxoethanoate derivatives has been shown (see Chapter 2, Section 2.3, Schemes 37 and 38) to afford fused 3,4-isoxazoles. It was therefore decided (Scheme 84) to prepare the diazo compound (293) and to study its decomposition in the expectation that it would afford the desired 2,1-benzisoxazole derivative (39b). The diazo compound (293) was readily prepared in good yield (77%) by the condensation of 2-nitrobenzoyl chloride (292) with ethyl diazoacetate. The pyrolysis of the diazo compound (293) in refluxing toluene was next examined and these conditions did afford the desired 2,1-benzisoxazole derivative (39b) however in only low yield (31%). Also produced under these conditions was a small amount (13%) of ethyl 2-(2-nitrophenyl)acetate (38b). An alternative procedure for the decomposition of the diazo compound (293) was next examined which involved irradiation with ultra-violet light since this technique is known[56] to promote the loss of nitrogen from diazo compounds. It was hoped that these conditions might afford a higher yield of the desired 2,1-benzisoxazole derivative (39b). However, irradiation of an ethanolic solution of the diazo compound (293) with light from a medium pressure mercury vapour lamp gave a complex mixture from which the only isolated product was a low yield (18%) of diethyl 2-(2-nitrophenyl)malonate (37b). Loss of nitrogen from the diazo compound is proposed to afford a carbene intermediate, the Wolff rearrangement of which would then give ethoxycarbonyl 2-nitrophenyl ketene. Trapping of this ketene with ethanol would then result in the formation of the observed product, diethyl 2-(2-nitrophenyl)malonate (37b). Since a complex mixture of unidentified products was produced from this photochemical reaction it was postulated that the diester (37b) is being formed in good yield but is unstable under the conditions employed. To investigate this assumption, an ethanolic solution of the diester (37b) was irradiated with ultra-violet light to acertain whether it does decompose under



(i) H_2O, room temp.

(ii) $SOCl_2$, reflux.

(iii) TsCl, pyridine, 0^0.

(iv) acetone, H_2O, reflux.

(v) AcOH, H_2O, 45^0.

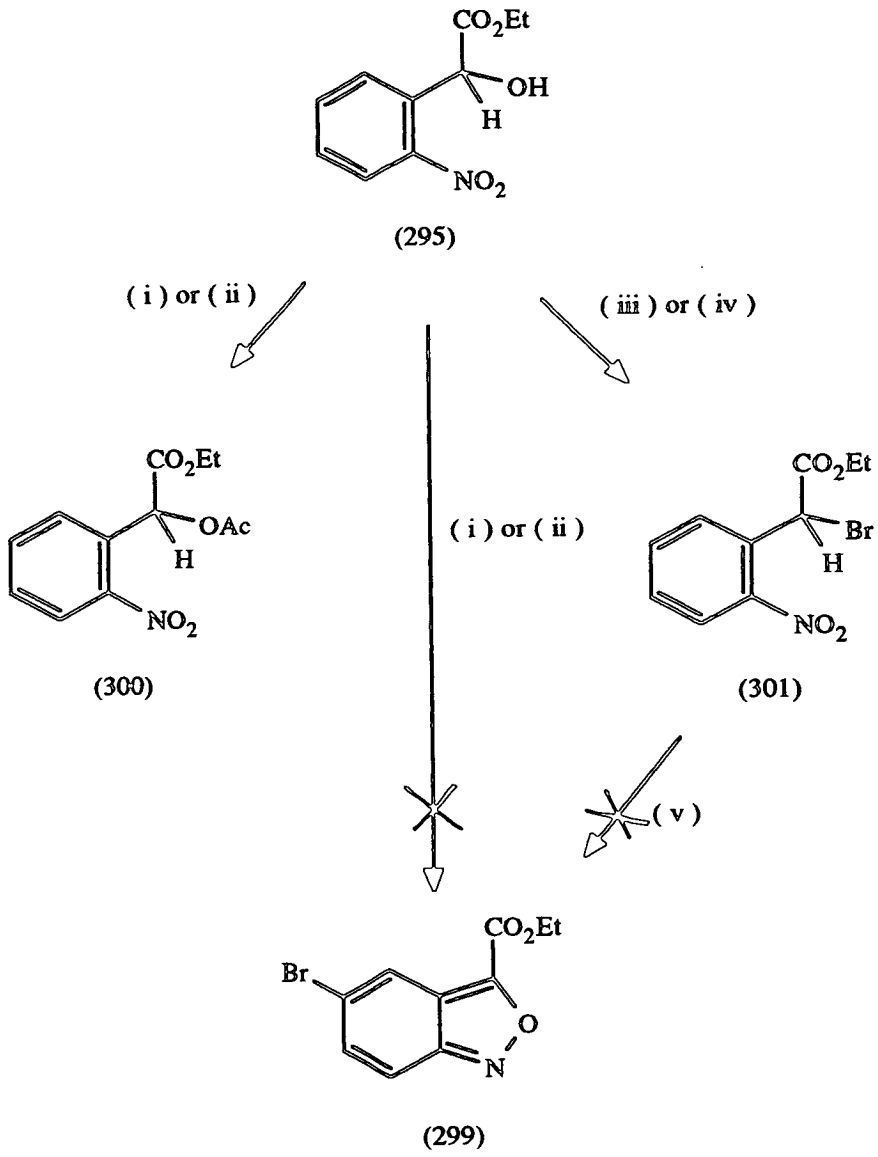
Scheme 85

these conditions. However, these conditions resulted in the isolation of only unreacted diester (37b) in good yield (88%). Next, in an attempt to avoid trapping of the proposed ketene intermediate with ethanol, a solution of the diazo compound (293) in acetonitrile was irradiated with ultra-violet light. Disappointingly, these conditions again gave only a complex mixture of products from which ethyl 2-(2-nitrophenyl) acetate (38b) was isolated in low yield (7%). Due to the disappointing results which were obtained, further investigations on the use of the diazo compound (293) as a precursor for 2,1-benzisoxazoles were not undertaken.

It was next decided to investigate various methods (Scheme 85) for the synthesis of 2,1-benzisoxazoles utilising as the starting material the known[136] 2-nitrobenzyl alcohol derivative (295). This alcohol (295) was readily available through hydrolysis of the known[136] imidate hydrochloride (294).

The action of thionyl chloride on the alcohol (295) was first investigated since the analogous methyl ester has been previously reported[6] to cyclise under these conditions to afford a good yield of methyl 5-chloro-2,1-benzisoxazole-3-carboxylate. Treatment of the alcohol (295) with thionyl chloride did afford the anticipated ethyl 5-chloro-2,1-benzisoxazole-3-carboxylate (296) however only in a disappointingly low yield (14%). The reason for the low yield of the ethyl ester (296) compared to that obtained for the analogous methyl ester[6] remains unclear at present.

It was then decided (Scheme 85) to synthesise the tosylate derivative (297) and to investigate whether it could be converted into a 2,1-benzisoxazole derivative. A literature report[5] states that, in an attempt to prepare 2-nitrobenzhydrol tosylate the desired product is unstable and decomposes to afford 2-nitrosobenzophenone. This latter compound has been further converted[10] into a 2,1-benzisoxazole derivative on treatment with hydrogen bromide. It was therefore anticipated that the tosylate derivative (297) could in some way be induced to form the nitroso compound (298) whose further conversion into the 2,1-benzisoxazole (299) could then be examined. The tosylate (297) was readily prepared in 41% yield by the reaction of the alcohol

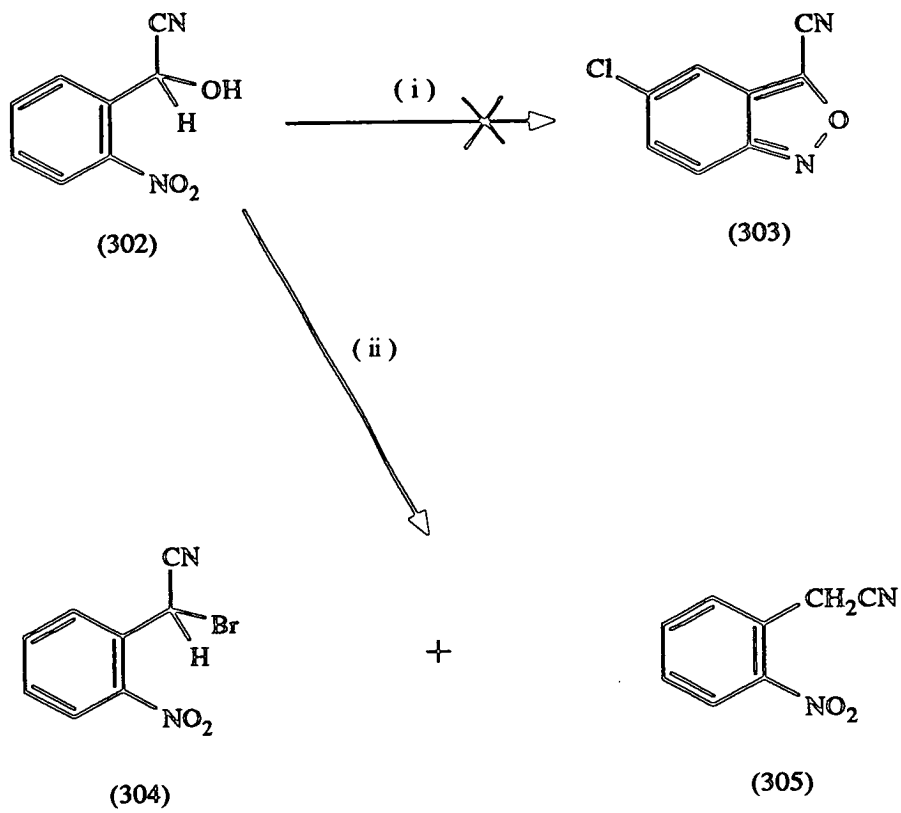


(i) HBr, AcOH, reflux.
(ii) AcBr, AcOH, reflux.
(iii) PBr_3, room temp.
(iv) PPh_3, CBr_4, MeCN, room temp.
(v) AcOH, reflux.

Scheme 86

(295) with tosyl chloride in the presence of pyridine. However, the attempted solvolysis of the tosylate (297) in either aqueous acetone or aqueous acetic acid failed to give the desired nitroso compound (298), both conditions giving only a good yield of unreacted starting material (297). An attempt was then made to prepare the triflate ester of the alcohol (295) since this derivative would be expected to be much less stable towards solvolysis than the corresponding tosylate derivative (297). However, the pyridine-catalysed reaction of trifluoromethanesulphonic anhydride with the alcohol (295) gave only an intractable mixture of products and therefore this reaction was not further investigated. Despite these previous failures, it was hoped (Scheme 86) that the 2-nitrobenzyl alcohol derivative (295) could be induced to cyclise on treatment with hydrogen bromide to afford the 5-bromo-2,1-benzisoxazole derivative (299). However, heating the alcohol (295) under reflux in 30% hydrogen bromide in acetic acid gave only a low yield (24%) of the undesired acetoxy compound (300). In a further attempt to synthesise the 2,1-benzisoxazole (299), a solution of the alcohol (295) in acetyl bromide and acetic acid was heated under reflux. However, these conditions afforded an excellent yield (92%) of the unwanted acetoxy compound (300).

Attempts to prepare (Scheme 86) the bromoacetate derivative (301) were next undertaken in the expectation that this compound would be converted by the action of heat into the 2,1-benzisoxazole (299). In practice, the action of neat phosphorus tribromide on the alcohol (295) afforded only a low yield (18%) of the desired bromoacetate (301) while using methylene chloride as co-solvent in this reaction resulted only in the formation of a complex mixture of products which were inseparable by flash-chromatography. In contrast, a moderate yield (43%) of the bromoacetate (301) was obtained through bromination of the alcohol (295) using carbon tetrabromide in the presence of triphenylphosphine and therefore further attempts to obtain a more efficient procedure were not undertaken. In any case, the thermal behaviour of the bromoacetate (301) proved to be disappointing since heating



(302) (303) (304) (305)

(i) $SOCl_2$, reflux.

(ii) PBr_3, CH_2Cl_2, room temp.

Scheme 87

this compound in acetic acid under reflux gave, after 3h, only unreacted starting material while, extension of the reaction time to 48h gave a complex, inseparable mixture of products. This line of research was therefore abandoned at this point.

Due to the failure of the 2-nitrobenzyl alcohol derivative (295) to provide an efficient route to 2,1-benzisoxazoles, the readily available[136] (Scheme 87) cyanohydrin derivative (302) was next investigated as an alternative precursor for these fused heterocycles. The reaction of the cyanohydrin (302) with thionyl chloride was attempted in the expectation of obtaining the 3-cyano-2,1-benzisoxazole (303). However, these conditions resulted in the isolation of only unreacted starting material (302). Next, attempts were made to prepare the bromoacetonitrile derivative (304) with a view to studying its possible conversion into a 2,1-benzisoxazole derivative. However, the bromination of the cyanohydrin (302) did not prove to be straightforward with only a 20% yield of the desired bromo compound (304) being formed on treatment of the cyanohydrin (302) with phosphorus tribromide in methylene chloride. Also produced under these conditions was a small amount (4%) of the known[137] 2-(2-nitrophenyl)acetonitrile (305). Attempts to improve the yield of the bromo compound (304) were unsuccessful. The reaction of the cyanohydrin (302) with neat phosphorus tribromide resulted only in the isolation of unreacted starting material while the attempted reaction with carbon tetrabromide in the presence of triphenylphosphine also proved unsuccessful, giving again only unreacted starting material. Due to these disappointing results further investigations on the use of the cyanohydrin (302) as a precursor for 2,1-benzisoxazoles were not undertaken.

4.2 : Experimental

General Experimental Details

For general experimental details see Chapter 2, Section 2.9, pages 80-81.

Elemental Analyses and Mass Spectroscopic Data

Elemental analyses and mass spectroscopic data are collected in Table 16, page 279.

Diethyl 2-(2-Nitrophenyl)propanedioates (37b) and (289)

A stirred suspension of sodium hydride (5.5g; 0.22mol) in anhydrous dimethylformamide (100ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (35.5g; 0.22mol) in anhydrous dimethylformamide (50.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min. The mixture was treated with a solution of the corresponding 2-halogenonitrobenzene derivative (0.1mol) in anhydrous dimethylformamide (50.0ml) and the resulting red solution was stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h then worked up as described for the individual reactions below.

(i) Diethyl 2-(2-Nitrophenyl)propanedioate (37b)

(a) The mixture from 2-chloronitrobenzene (284a) was diluted with water (20.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (125ml). The resulting mixture was extracted with methylene chloride (3 x 200ml) to give an orange oil (34.0g) which was dissolved in diethyl ether (100ml) and the resulting solution was extracted with 2M aqueous sodium hydroxide (10 x 100ml). The alkaline extracts were acidified with concentrated

hydrochloric acid and then extracted with diethyl ether (2 x 500ml) to give a red oil (19.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted 2-chloronitrobenzene (284a) (7.9g; 50%) as a yellow solid, m.p. 27-32° (lit.,[138] 33°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (9:1) afforded diethyl 2-(2-nitropheyl)propanedioate (37b) (5.3g; 19%) which formed colourless needles, m.p. 47° (from ethanol), ν_{max} 1728 (C=O) and 1528 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.10-8.00 (1H, m, ArH), 7.63-7.44 (3H, m, 3 x ArH), 5.27 (1H, s, CH), 4.25 (4H, q, J = 7 Hz, 2 x CH_2) and 1.26 (6H, t, J = 7 Hz, 2 x CH_3).

Final elution with methanol gave only a complex brown solid (0.66g) which was not further investigated.

(b) The mixture from 2-fluoronitrobenzene (284b) was diluted with water (20.0ml) and stirred at room temperature for 10min then rotary evaporated and the residue treated with water (150ml). The precipitated solid was then collected to afford diethyl 2-(2-nitropheyl)propanedioate (37b) (28.9g; 100%) as a pale yellow solid, m.p. 49-50°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

(ii) Diethyl 2-[2-Nitro-4-(trifluoromethyl)phenyl]propanedioate (289)

The mixture from 4-chloro-3-nitro(trifluoromethyl)benzene (288) was diluted with water and stirred at room temperature for 10min then rotary evaporated and the residue treated with water. The mixture was acidified with concentrated hydrochloric acid and extracted with methylene chloride to give an orange oil which was distilled to afford diethyl 2-[2-nitro-4-(trifluoromethyl)phenyl]propanedioate (289) (90%) as a yellow oil, b.p. 90-96°/ 0.4mmHg, ν_{max} 1755 and 1735 (C=O) and 1545 and 1330

(NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.30-8.28 (1H, m, ArH), 7.85-7.65 (2H, m, 2 x ArH), 5.32 (1H, s, CH), 4.26 (4H, q, J = 7 Hz, 2 x CH_2) and 1.27 (6H, t, J = 7 Hz, 2 x CH_3).

Attempted Pyrolysis Reactions of Diethyl 2-(2-Nitrophenyl)propanedioate (37b)

(a) Diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.56g; 0.002mol) was heated under high vacuum at 164°/1.5mmHg in a kugelrohr apparatus. After 0.5h a yellow oil had distilled which rapidly solidified to give unreacted diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.32g; 57%) as a yellow solid, m.p. 47-48°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.56g; 0.002mol) in anhydrous xylene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 48h.

Rotary evaporation of the mixture gave a brown oil (0.55g) whose t.l.c. in hexane-ethyl acetate (3:1) over silica showed it to contain mainly unreacted diethyl 2-(2-nitrophenyl)propanedioate (37b) by comparison with an authentic sample.

(c) A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.56g; 0.002mol) in dibenzyl ether (5.0ml) was stirred and heated at 190° (oil bath) with exclusion of atmospheric moisture for 1h.

The mixture was allowed to cool to room temperature then flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave dibenzyl ether (4.8g) as a pale yellow oil identical (t.l.c. in methylene chloride over silica) to an authentic sample.

Elution with hexane-ethyl acetate (4:1) gave unreacted diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.50g; 89%) as an orange oil identified by

comparison (i.r. spectrum and t.l.c. in methylene chloride over silica) with an authentic sample.

Final elution with methanol gave only a negligible amount of material.

Pyrolysis Reactions of Diethyl 2-(2-Nitrophenyl)propanedioate (37b)

(a) A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.56g; 0.002mol) in dibenzyl ether (5.0ml) was stirred and heated at 250° (oil bath) with exclusion of atmospheric moisture for 1h.

The mixture was allowed to cool to room temperature then flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) and then with hexane-ethyl acetate (4:1) gave a series of multicomponent oils and gums (total 5.3g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed them to contain mainly dibenzyl ether by comparison with an authentic sample.

Elution with hexane-ethyl acetate (3:2) gave a red semi-solid which was washed with a little diethyl ether to afford 1H-indole-2,3-dione (287) (0.04g; 14%) as a red solid, m.p. 197-202° (lit.,[139] 203.5°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Elution with methanol gave only an intractable brown gum (0.02g).

(b) A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (1.4g; 0.005mol) in anhydrous mesitylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

The mixture was rotary evaporated to give a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (19:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and gums (total 1.3g) from which no identifiable material could be obtained.

Ethyl 2,1-Benzisoxazole-3-carboxylate (39b)

A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (14.1g; 0.05mol) in anhydrous xylene (500ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 100h.

The mixture was rotary evaporated to give a brown gum (10.9g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a series of multicomponent yellow oils (total 0.86g) from which no identifiable material could be obtained.

Further elution with hexane-ethyl acetate (9:1) afforded ethyl 2,1-benzisoxazole-3-carboxylate (39b) (6.0g; 63%) which formed colourless needles, m.p. 61-62° (from hexane) (lit.,[16] 66-67°), ν_{max} 1720-1700 br (C=O) cm^{-1}, δ_H ($CDCl_3$) 7.93-6.83 (4H, m, 4 x ArH), 4.50 (2H, q, J = 7 Hz, CH_2) and 1.45 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (9:1) gave some unreacted diethyl 2-(2-nitrophenyl)propanedioate (37b) (2.2g; 16%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (3:1) over silica] with an authentic sample.

Final elution with methanol gave an intractable brown oil (2.2g) which was not further investigated.

The Pyrolysis of Diethyl 2-[2-Nitro-4-(trifluoromethyl)phenyl]propanedioate (289)

A solution diethyl 2-[2-nitro-4-(trifluoromethyl)phenyl]propanedioate (289) (3.5g; 0.01mol) in anhydrous xylene (100ml) was stirred and heated under reflux with

exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

The mixture was rotary evaporated to give a orange oil (3.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (19:1) afforded ethyl 6-(trifluoromethyl)-2,1-benzisoxazole-3-carboxylate (290) (0.67g; 26%) as pale yellow plates, m.p. 80-83°, b.p. 138°/ 0.6mmHg, ν_{max} 1720 (C=O) cm^{-1}, δ_H ($CDCl_3$) 8.13-8.00 (2H, m, 2 x ArH), 7.34 (1H, dd, J = 9 and 1 Hz, ArH), 4.55 (2H, q, J = 7 Hz, CH_2) and 1.49 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (19:1) gave a series of multicomponent orange oils (total 1.7g) which were combined and kugelrohr distilled to afford some unreacted diethyl 2-[2-nitro-4-(trifluoromethyl)phenyl]propanedioate (289) (0.28g; 8%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (4:1) over silica] with an authentic sample, followed by ethyl 2-[2-nitro-4-(trifluoromethyl)phenyl]ethanoate (291) which formed pale yellow needles, m.p. 56-58°, ν_{max} 1730 (C=O) and 1540 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.35 (1H, d, J = 2 Hz, ArH), 7.83 (1H, dd, J = 8 and 2 Hz, ArH), 7.50 (1H, d, J = 8 Hz, ArH), 4.17 (2H, q, J = 7 Hz, CH_2), 4.07 (2H, s, CH_2) and 1.24 (3H, t, J = 7 Hz, CH_3), and leaving an involatile residual orange gum (0.42g).

Elution with hexane-ethyl acetate (4:1) and then finally with methanol gave only a series of multicomponent oils and gums (total 0.49g) which were not further investigated.

Ethyl 2-(2-Nitrophenyl)ethanoate (38b)

A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (2.8g; 0.01mol) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 24h.

The mixture was rotary evaporated and the residue dissolved in methylene chloride (50.0ml). The extracts were then washed with 2M aqueous hydrochloric acid

(10.0ml) and rotary evaporated to afford ethyl 2-(2-nitrophenyl)ethanoate (38b) (1.6g; 76%) which formed colourless needles, m.p. 62-63° (from ethanol) (lit.,[141] 64-65°), ν_{max} 1728 (C=O) and 1528 and 1345 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.13-8.02 (1H, m, ArH), 7.66-7.26 (3H, m, 3 x ArH), 4.15 (2H, q, J = 7 Hz, CH_2), 3.99 (2H, s, CH_2) and 1.23 (3H, t, J = 7 Hz, CH_3).

The Attempted Pyrolysis of Diethyl 2-Phenylpropanedioate in Aqueous Pyridine Solution

A solution of diethyl 2-phenylpropanedioate (2.4g; 0.01mol) in pyridine (18.0ml) and water (2.0ml) was stirred and heated under reflux for 24h.

The mixture was rotary evaporated and the residue dissolved in methylene chloride (25.0ml). The extracts were then washed with 2M aqueous hydrochloric acid (5.0ml) and rotary evaporated to give only unreacted diethyl 2-phenylpropanedioate (2.1g; 88%) identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (4:1) over silica] to an authentic sample.

Diethyl 2-(4-Nitrophenyl)propanedioate

A stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of diethyl propanedioate (17.6g; 0.11mol) in anhydrous dimethylformamide (25.0ml) and the resulting mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15min. The mixture was treated with a solution of 4-fluoronitrobenzene (7.1g; 0.05mol) in anhydrous dimethylformamide (25.0ml) and the resulting red solution stirred and heated at 100° (oil-bath) with exclusion of atmospheric moisture for 1h.

The mixture was diluted with water (10.0ml) and stirred at room temperature for 10 min then rotary evaporated and the residue treated with water (75.0ml). The

mixture was acidified with 2M aqueous hydrochloric acid and the precipitated solid was then collected and crystallised from ethanol to afford diethyl 2-(4-nitrophenyl) propanedioate (7.7g; 55%) as yellow needles, m.p. 57-59° (lit., [140] 56-57°), ν_{max} 1735 (C=O) and 1523 and 1348 (NO_2) cm^{-1}.

The Attempted Pyrolysis of Diethyl 2-(4-Nitrophenyl)propanedioate

A solution diethyl 2-(4-nitrophenyl)propanedioate (2.8g; 0.01mol) in anhydrous xylene (100ml) was stirred and heated under reflux with exclusion of atmospheric moisture and with cycling of the solvent through a soxhlet extractor containing anhydrous 5A molecular sieves (30g) for 48h.

The mixture was rotary evaporated to give only unreacted diethyl 2-(4-nitrophenyl)propanedioate (2.7g; 96%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (3:1) over silica] with an authentic sample.

The Catalytic Reduction of Ethyl 2,1-Benzisoxazole-3-carboxylate (39b)

A solution of ethyl 2,1-benzisoxazole-3-carboxylate (39b) (0.96g; 0.005mol) in ethyl acetate (25.0ml) was hydrogenated over 10% palladium-on-charcoal (0.10g) at room temperature and atmospheric pressure for 3h.

The mixture was filtered through celite and the filtrate was rotary evaporated to give a yellow oil (0.70g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (24:1) afforded ethyl 4,5,6,7-tetrahydro-2,1-benzisoxazole-3-carboxylate (285) (0.39g; 40%) which formed colourless needles, m.p. 65-66° (from pentane), ν_{max} 1715 (C=O) cm^{-1}, δ_H ($CDCl_3$) 4.39 (2H, q, J = 7 Hz, CH_2), 2.85-2.69 (4H, m, 2 x CH_2), 1.84-1.63 (4H, m, 2 x CH_2) and 1.38 (3H, t, J = 7 Hz, CH_3), δ_C ($CDCl_3$) 161.8 (quat), 152.5 (quat), 121.6 (quat), 61.5 (CH_2), 21.7 (CH_2), 21.7 (CH_2), 21.5 (CH_2), 20.4 (CH_2), 14.1 (CH_3).

Elution with methanol afforded 1H-indole-2,3-dione (287) (0.065g; 9%) as an orange solid, m.p. 180-185° (lit.,[139] 203.5°), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with an authentic sample.

Further elution with methanol gave only a complex brown gum (0.19g) which was not further investigated.

2-Nitrobenzoyl Chloride (292)

A sample of 2-nitrobenzoyl chloride (292) was kindly supplied by Mr. K.S. Currie, Department of Chemistry, University of Edinburgh.

Ethyl 2-Diazo-3-(2-nitrophenyl)-3-oxopropanoate (293)

2-Nitrobenzoyl chloride (292) (1.9g; 0.01mol) was added in one portion with stirring to ethyl 2-diazoethanoate (2.3g; 0.02mol) at 10° (ice bath) and the yellow solution was stirred and heated at 50° (oil bath) with exclusion of atmospheric moisture for 19h.

The mixture was rotary evaporated to give a yellow oil (3.6g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (9:1) gave a multicomponenet, yellow oil (0.06g) which was not further investigated.

Elution with hexane-diethyl ether (4:1) afforded ethyl 2-diazo-3-(2-nitrophenyl) -3-oxopropanoate (293) (2.0g; 77%) which formed cream, irregular crystals, m.p. 62-63° (from ethanol), ν_{max} 2149 (C=$\overset{+}{N}$=$\overset{-}{N}$), 1719 and 1640 (C=O) and 1530 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.25-8.13 (1H, m, ArH), 7.80-7.30 (3H, m, 3 x ArH), 4.09 (2H, q, J = 7 Hz, CH_2) and 1.12 (3H, t, J = 7 Hz, CH_3).

Final elution with methanol gave a small amount of a multicomponent yellow oil which was not further investigated.

The Pyrolysis of Ethyl 2-Diazo-3-(2-nitrophenyl)-3-oxopropanoate (293)

A solution of ethyl 2-diazo-3-(2-nitrophenyl)-3-oxopropanoate (293) (0.53g; 0.002mol) in anhydrous toluene (10.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 11h.

The mixture was rotary evaporated to give a brown gum (0.46g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (19:1) afforded ethyl 2,1-benzisoxazole-3-carboxylate (39b) (0.12g; 31%) as a colourless solid, m.p. 53-59°, identified by comparison (m.p., mixed m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-diethyl ether (9:1) afforded ethyl 2-(2-nitrophenyl) ethanoate (38b) (0.052g; 13%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-diethyl ether (1:1) over silica] with an authentic sample.

Elution with hexane-diethyl ether (4:1) through to diethyl ether and then finally with methanol gave only a series of intractable oils and gums (total 0.13g) which were not further investigated.

Photochemical Reactions of Ethyl 2-Diazo-3-(2-nitrophenyl)-3-oxopropanoate (293)

(a) A solution of ethyl 2-diazo-3-(2-nitrophenyl)-3-oxopropanoate (293) (0.53g; 0.002mol) in anhydrous ethanol (180ml) was irradiated for 4h under a nitrogen atmosphere in a Hanovia medium pressure photochemical reactor.

Rotary evaporation of the mixture gave a brown gum (0.47g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (4:1) afforded diethyl 2-(2-nitrophenyl)propanedioate (37b) (0.10g; 18%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-diethyl ether (1:1) over silica] with a sample prepared previously.

Elution with hexane-diethyl ether (7:3) through to diethyl ether and then finally with methanol gave only a series of intractable gums and solids (total 0.17g) from which no identifiable material could be obtained.

(b) A solution of ethyl 2-diazo-3-(2-nitrophenyl)-3-oxopropanoate (293) (1.3g; 0.005mol) in anhydrous acetonitrile (180ml) was irradiated for 4h under a nitrogen atmosphere in a Hanovia medium pressure photochemical reactor.

Rotary evaporation of the mixture gave a brown oil (1.2g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (9:1) afforded ethyl 2-(2-nitrophenyl) ethanoate (38b) (0.075g; 7%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-diethyl ether (1:1) over silica] with a sample prepared previously.

Elution with hexane-diethyl ether (4:1) gave unreacted ethyl 2-diazo-3-(2-nitrophenyl)-3-oxopropanoate (293) (0.27g; 21%) as a brown oil identified by comparison [i.r. spectrum and t.l.c. in hexane-diethyl ether (1:1) over silica] with an authentic sample.

Elution with hexane-diethyl ether (7:3) through to diethyl ether and then finally with methanol gave only a series of intractable gums (total 0.65g) from which no identifiable material could be obtained.

<u>The Attempted Photochemical Reaction of Diethyl 2-(2-Nitrophenyl)propanedioate (37b)</u>

A solution of diethyl 2-(2-nitrophenyl)propanedioate (37b) (1.4g; 0.005mol) in anhydrous ethanol (180ml) was irradiated for 20h under a nitrogen atmosphere in a Hanovia medium pressure photochemical reactor.

Rotary evaporation of the mixture gave only unreacted diethyl 2-(2-nitrophenyl)propanedioate (37b) (1.2g; 88%) as a yellow solid, m.p. 43-47°, identical (m.p. and i.r. spectrum) to an authentic sample.

Ethyl 2-Hydroxy-2-(2-nitrophenyl)acetimidate Hydrochloride (294)

A sample of ethyl 2-hydroxy-2-(2-nitrophenyl)acetimidate hydrochloride (294) was kindly supplied by Dr. M. Scobie, Department of Chemistry, University of Edinburgh.

Ethyl 2-Hydroxy-2-(2-nitrophenyl)ethanoate (295)

A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)acetimidate hydrochloride (294) (13.0g; 0.05mol) in water (100ml) was stirred at room temperature for 2h.

The suspended solid was then collected to afford ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (9.5g; 85%) as a colourless solid, m.p. 47-50° (lit.,[136] 49-50°), ν_{max} 1710 (C=O) and 1521 and 1351 (NO_2) cm^{-1}.

The Reaction of Ethyl 2-Hydroxy-2-(2-nitrophenyl)ethanoate (295) with Thionyl Chloride

A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in thionyl chloride (5.0ml) was stirred at room temperature for 16h and then heated under reflux with exclusion of atmospheric moisture for 0.5h.

Rotary evaporation of the mixture gave a brown oil (1.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded ethyl 5-chloro-2,1-benzisoxazole-3-carboxylate (296) (0.15g; 14%) which formed colourless needles, m.p. 83-84° (from methanol), ν_{max} 1720 (C=O) cm^{-1}, δ_H ($CDCl_3$) 7.91 (1H, dd, J = 2 and 1 Hz, ArH), 7.68 (1H, dd, J = 10 and 1 Hz, ArH), 7.31 (1H, dd, J = 10 and 2 Hz, ArH), 4.54 (2H, q, J = 7 Hz, CH_2) and 1.49 (3H, t, J = 7 Hz, CH_3).

Further elution with hexane-ethyl acetate (9:1) gave a complex, orange oil (0.09g) which was not further investigated.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (0.56g; 51%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] with an authentic sample.

Final elution with methanol gave only a small amount (0.20g) of an intractable brown tar.

Ethyl 2-(2-Nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297)

A stirred solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in anhydrous pyridine (2.5ml) was cooled to 0° (ice-salt bath) and treated portionwise with freshly crystallised toluene-4-sulphonyl chloride (1.05g; 0.0055mol) and the resulting solution was kept at 5° (refrigerator) with exclusion of atmospheric moisture for 20h.

The mixture was treated with ice (10.0g) and 2M aqueous hydrochloric acid (10.0ml) and the resulting solution was extracted with diethyl ether (3 x 20.0ml) to give a cream solid. This was crystallised from diethyl ether to afford ethyl 2-(2-nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297) (0.77g; 41%) which formed colourless crystals, m.p. 74-75° (from diethyl ether), ν_{max} 1744 (C=O) and 1527 and 1354 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.08-7.28 (8H, m, 8 x ArH), 6.64 (1H, s, CH), 4.09 (2H, q, J = 7 Hz, CH_2), 2.43 (3H, s, CH_3) and 1.11(3H, t, J = 7 Hz, CH_3).

Rotary evaporation of the ethereal mother liquor gave a yellow oil (0.33g) whose t.l.c. in hexane-ethyl acetate (7:3) over silica showed it to be a three component mixture which therefore was not further investigated.

Attempted Solvolysis Reactions of Ethyl 2-(2-Nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297)

(a) A solution of ethyl 2-(2-nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297) (0.76g; 0.002mol) in acetone (9.0ml) and water (1.0ml) was stirred and heated under reflux for 3h.

The mixture was rotary evaporated, the residue treated with water (5.0ml) and the resulting mixture was extracted with methylene chloride (3 x 10.0ml) to give only unreacted ethyl 2-(2-nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297) (0.65g; 86%) as a cream solid, m.p. 71-74°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of ethyl 2-(2-nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297) (0.76g; 0.002mol) in glacial acetic acid (9.0ml) and water (1.0ml) was stirred and heated at 50° (oil bath) for 6h.

The mixture was rotary evaporated to give only unreacted ethyl 2-(2-nitrophenyl)-2-(toluene-4-sulphonyloxy)ethanoate (297) (0.65g; 86%) as a cream solid, m.p. 70-73°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of Ethyl 2-Hydroxy-2-(2-nitrophenyl)ethanoate (295) with Trifluoromethanesulphonic Anhydride

A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) and anhydrous pyridine (0.79g; 0.01mol) in anhydrous methylene chloride (10.0ml) was stirred under nitrogen and cooled to -15° (ice-acetone bath) then treated dropwise over 45 min with a solution of trifluoromethanesulphonic anhydride (1.6g; 0.0055mol) in anhydrous methylene chloride (10.0ml). The resulting solution was then stirred at room temperature under nitrogen for a further 15 min.

The mixture was treated with water (10.0ml) and extracted with methylene chloride (3 x 10.0ml) to give a dark brown gum (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent gums (total 1.1g) from which no identifiable material was obtained.

Ethyl 2-Acetoxy-2-(2-nitrophenyl)ethanoate (300)

(a) Ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) was added to a 30% w/w solution of hydrogen bromide in glacial acetic acid (10.0ml) and the resulting mixture was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

The mixture was rotary evaporated, the residue was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0ml) and the resulting mixture extracted with methylene chloride (3 x 10.0ml) to afford ethyl 2-acetoxy-2-(2-nitrophenyl)ethanoate (300) (0.32g; 24%) which formed colourless needles, m.p. 67-69° (from ethanol), ν_{max} 1739 (C=O) and 1530 and 1344 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.05-7.44 (4H, m, 4 x ArH), 6.80 (1H, s, CH), 4.16 (2H, q, J = 7 Hz, CH_2), 2.16 (3H, s, CH_3) and 1.17 (3H, t, J = 7 Hz, CH_3).

Acidification of the aqueous phase with 2M aqueous hydrochloric acid followed by extraction with methylene chloride (3 x 10.0ml) gave no further material.

Neutralisation of the aqueous phase with solid sodium acetate followed by extraction with methylene chloride (3 x 10.0ml) gave no further material.

(b) A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in glacial acetic acid (7.5ml; 0.125mol) and acetyl bromide (10.0ml;

0.125mol) was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

Rotary evaporation of the mixture afforded ethyl 2-acetoxy-2-(2-nitrophenyl)ethanoate (300) (1.2g; 92%) as an orange oil identified by comparison [i.r. and ^1H n.m.r. spectra and t.l.c. in hexane-ethyl acetate (7:3) over silica] with a sample prepared previously.

Ethyl 2-Bromo-2-(2-nitrophenyl)ethanoate (301)

(a) A suspension of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in phosphorus tribromide (4.1g; 0.015mol) was stirred at room temperature with exclusion of atmospheric moisture for 2h.

Excess phosphorus tribromide was removed by passing a current of air through the reaction mixture to give a pale orange oil (2.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded ethyl 2-bromo-2-(2-nitrophenyl)ethanoate (301) (0.26g; 18%) as a pale yellow oil, b.p. 105-110°/ 0.1mmHg, ν_{max} 1740 (C=O) and 1529 and 1348 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.06-7.38 (4H, m, 4 x ArH), 6.05 (1H, s, CH), 4.25 (2H, q, J = 7 Hz, CH_2) and 1.28 (3H, t, J = 7 Hz, CH_3).

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (0.43g; 39%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] with a sample prepared previously.

Final elution with methanol gave an intractable, multicomponent orange gum (0.86g) which was not further investigated.

(b) A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in anhydrous acetonitrile (10.0ml) was stirred under nitrogen and treated with triphenylphosphine (1.4g; 0.0055mol) and the mixture was cooled to 5° (ice-water bath). A solution of carbon tetrabromide (1.8g; 0.0055mol) in anhydrous acetonitrile (5.0ml) was then added dropwise and the resulting mixture stirred at room temperature under nitrogen for 22h.

Rotary evaporation of the mixture gave a yellow oil (2.8g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded ethyl 2-bromo-2-(2-nitrophenyl)ethanoate (301) (0.62g; 43%) as a pale yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] with a sample prepared previously.

Elution with hexane-ethyl acetate (4:1) gave unreacted ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (0.39g; 35%) as a yellow oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] with a sample prepared previously.

Final elution with methanol gave an complex orange gum (0.80g) which was not further investigated.

The Attempted Reaction of Ethyl 2-Hydroxy-2-(2-nitrophenyl)ethanoate (295) with Phosphorous Tribromide in Methylene Chloride

A solution of ethyl 2-hydroxy-2-(2-nitrophenyl)ethanoate (295) (1.1g; 0.005mol) in anhydrous methylene chloride (10.0ml) was treated with phosphorus tribromide (4.1g; 0.015mol) and the resulting solution was stirred at room temperature with exclusion of atmospheric moisture for 2h.

Rotary evaporation of the mixture gave an orange oil (2.0g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to ethyl acetate and then finally with methanol gave only a series of multicomponent oils and solids (total 1.2g) which were not further investigated.

Attempted Cyclisation Reactions of Ethyl 2-Bromo-2-(2-nitrophenyl)ethanoate (301)

(a) A solution of ethyl 2-bromo-2-(2-nitrophenyl)ethanoate (301) (0.58g; 0.002mol) in glacial acetic acid (5.0ml) was stirred and heated under reflux with exclusion of atmospheric moisture for 3h.

Rotary evaporation of the mixture gave only unreacted ethyl 2-bromo-2-(2-nitrophenyl)ethanoate (301) (0.51g; 88%) as an orange oil identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (7:3) over silica] with an authentic sample.

(b) Repetition of the above reaction with heating under reflux for 48h gave, after rotary evaporation of the reaction mixture, a complex brown gum (0.44g) whose t.l.c. in hexane-ethyl acetate (7:3) over silica showed it to be an eight component mixture which therefore was not further investigated.

2-Hydroxy-2-(2-nitrophenyl)ethanenitrile (302)

A sample of 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) was kindly supplied by Dr. M. Scobie, Department of Chemistry, University of Edinburgh.

The Attempted Reaction of 2-Hydroxy-2-(2-nitrophenyl)ethanenitrile (302) with Thionyl Chloride

A solution of 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (0.89g; 0.005mol) in thionyl chloride (10.0ml) was stirred at room temperature for 0.5h and then under reflux with exclusion of atmospheric moisture for 0.5h.

Rotary evaporation of the mixture gave an orange oil (1.1g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (9:1) gave an unidentified yellow solid (0.08g), m.p. 56-58°, ν_{max} 1532 and 1346 (NO_2) cm^{-1}.

Elution with hexane-diethyl ether (7:3) gave unreacted 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (0.46g; 52%) as a cream solid, m.p. 97-98° (lit.,[136] 95°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with hexane-diethyl ether (1:1) gave a multicomponent brown gum (0.31g) which was not further investigated.

Final elution with methanol gave no further material.

Attempted Bromination Reactions of 2-Hydroxy-2-(2-nitrophenyl)ethanenitrile (302)

(a) A solution of 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (1.8g; 0.01mol) in phosphorus tribromide (8.1g; 0.03mol) was stirred at room temperature with exclusion of atmospheric moisture for 2h.

The mixture was rotary evaporated and the residue triturated with hexane to give unreacted 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (1.8g; 100%) as a cream solid, m.p. 93-95° (lit.,[136] 95°), identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (1.8g; 0.01mol) in anhydrous acetonitrile (20.0ml) was stirred under nitrogen and was treated with triphenylphosphine (2.9g; 0.011mol) and the mixture was cooled to 5° (ice-water bath). A solution of carbon tetrabromide (3.7g; 0.011mol) in anhydrous acetonitrile (10.0ml) was added dropwise and the resulting mixture was stirred at room temperature under nitrogen for 19h.

Rotary evaporation of the mixture gave a brown gum (7.8g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave only a series of multicomponent orange oils (total 0.51g) which were not further investigated.

Elution with hexane-ethyl acetate (4:1) gave only unreacted 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (1.3g ;69%) as a cream solid, m.p. 94-96° (lit.,[136] 95°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with hexane-ethyl acetate (1:1) and then finally with methanol gave only a series of dark multicomponent oils (total 4.1g) which were not further investigated.

The Reaction of 2-Hydroxy-2-(2-nitrophenyl)ethanenitrile (302) with Phosphorus Tribromide

A solution of 2-hydroxy-2-(2-nitrophenyl)ethanenitrile (302) (1.8g; 0.01mol) in anhydrous methylene chloride (20.0ml) was treated with phosphorus tribromide (8.1g; 0.03mol) and the resulting solution was stirred at room temperature with exclusion of atmospheric moisture for 3h.

Filtration of the reaction mixture gave an intractable yellow solid (0.60g), m.p. 115-130° (decomp.), from which no identifiable material could be obtained.

Rotary evaporation of the organic mother liquor gave an orange gum (1.8g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) afforded 2-bromo-2-(2-nitrophenyl) ethanenitrile (304) (0.48g; 20%) which formed colourless, irregular crystals, m.p. 71-72° (from ethanol), ν_{max} 1525 and 1345 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.21 -7.51 (4H, m, 4 x ArH) and 6.54 (1H, s, CH).

Further elution with hexane-ethyl acetate (9:1) afforded 2-(2-nitrophenyl) ethanenitrile (305) (0.07g; 4%) which formed colourless needles, m.p. 82-83° (from ethanol) (lit.,[137] 84°), ν_{max} 2242 (CN) and 1522 and 1343 (NO_2) cm^{-1}.

Final elution with methanol gave an intractable, dark brown gum (1.2g) from which no identifiable material was obtained.

Table 16 : Elemental Analyses and Mass Spectroscopic Data

Compound	Found				Required			
	C%	H%	N%	M^+, $(M+H)^+$ [a]	C%	H%	N%	M, $(M+H)^+$ [a]
(37b) ($C_{13}H_{15}NO_6$)	55.5	5.3	5.1	(282)	55.5	5.3	5.0	281
(38b) ($C_{10}H_{11}NO_4$)	57.3	5.2	6.7	(210)	57.4	5.3	6.7	209
(39b) ($C_{10}H_9NO_3$)	62.3	4.7	7.2	191	62.3	4.7	7.3	191
(285) ($C_{10}H_{13}NO_3$)	61.5	6.5	6.9	195	61.5	6.7	7.2	195
(289) ($C_{14}H_{14}F_3NO_6$)	48.2	4.3	4.0	(350)	48.1	4.0	4.0	349
(290) ($C_{11}H_8F_3NO_3$)	52.1	3.3	5.2	259.0466	51.0	3.1	5.4	259.0456
(291) ($C_{11}H_{10}F_3NO_4$)	47.8	3.8	5.0	(278)	47.7	3.6	5.0	277
(293) ($C_{11}H_9N_3O_5$)	50.2	3.5	16.1	(264)	50.2	3.4	16.0	263
(296) ($C_{10}H_8ClNO_3$)	53.1	3.6	6.2	(228), (226)	53.2	3.6	6.2	227, 225
(297) ($C_{17}H_{17}NO_7S$)	54.2	4.6	3.7	(380)	53.8	4.5	3.7	379
(300) ($C_{12}H_{13}NO_6$)	54.0	5.0	5.3	(268)	53.9	4.9	5.2	267
(301) ($C_{10}H_{10}BrNO_4$)	42.6	3.6	5.0	289.9852, 287.9872	41.7	3.5	4.9	289.9852, 287.9872
(304) ($C_8H_5BrN_2O_2$)	39.9	2.1	11.6	(243), (241)	39.8	2.1	11.6	242, 240
(305) ($C_8H_6N_2O_2$)	58.9	3.8	17.1	-	59.2	3.7	17.3	162

a, molecular ions detected by Electron Impact Mass Spectroscopy or, for values in parentheses, molecular ions detected by Fast Atom Bombardment Mass Spectroscopy.

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